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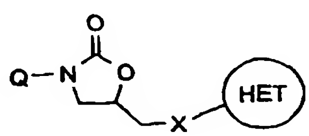
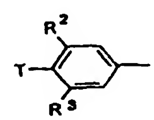
(54) Title: OXAZOLIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)



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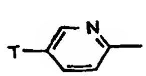

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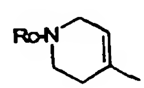

(TC5)

(57) Abstract

Compounds of formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof, wherein, for example, X is –O– or –S–; HET is an optionally substituted C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S; Q is selected from, for example, formulae (Q1) and (Q2); R^2 and R^3 are independently hydrogen or fluoro; T is selected from a range of groups, for example, an N-linked (fully unsaturated) 5-membered heteroaryl ring system or a group of formula (TC5) wherein Rc is, for example, $R^{13}CO$–, $R^{13}SO_2$– or $R^{13}CS$–; wherein R^{13} is, for example, optionally substituted (1–10C)alkyl or $R^{14}C(O)O$(1–6C)alkyl wherein R^{14} is optionally substituted (1–10C)alkyl; are useful as antibacterial agents; and processes for their manufacture and pharmaceutical compositions containing them are described.

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CHEMICAL COMPOUNDS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing a substituted oxazolidinone ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly good activity against such pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

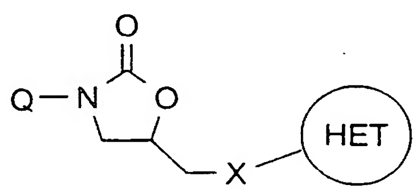
The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with nephrotoxicity and ototoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens.

Certain antibacterial compounds containing an oxazolidinone ring have been described in the art (for example, Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165). Such antibacterial oxazolidinone compounds with a 5-methylacetamide sidechain may be subject to mammalian peptidase metabolism. Furthermore, bacterial resistance to known antibacterial agents may develop, for

example, by (i) the evolution of active binding sites in the bacteria rendering a previously active pharmacophore less effective or redundant, and/or (ii) the evolution of means to chemically deactivate a given pharmacophore. Therefore, there remains an ongoing need to find new antibacterial agents with a favourable pharmacological profile, in particular for compounds containing new pharmacophores.

We have discovered a class of antibiotic compounds containing a new class of substituted oxazolidinone ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams.

Accordingly the present invention provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

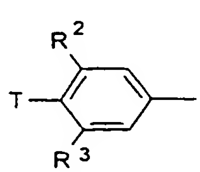


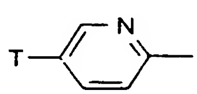
(I)

wherein X is -O-, -S-, -SO- or $-SO_2-$;

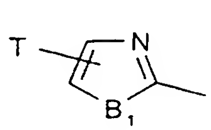
HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

Q is selected from Q1 to Q9 :-

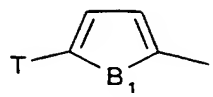




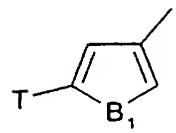
Q1 Q2



Q3



Q4



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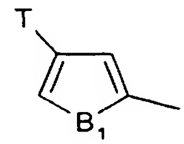

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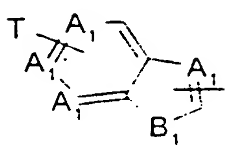
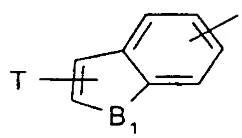
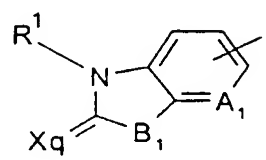


Q7



Q8



Q9

wherein R^2 and R^3 are independently hydrogen or fluoro;

wherein A_1 is carbon or nitrogen; B_1 is O or S (or, in Q9 only, NH); X_q is O, S or N-R^1 (wherein R^1 is hydrogen, (1-4C)alkyl or hydroxy-(1-4C)alkyl); and wherein in Q7 each A_1 is independently selected from carbon or nitrogen, with a maximum of 2 nitrogen heteroatoms in the 6-membered ring, and Q7 is linked to T via any of the A_1 atoms (when A_1 is carbon), and linked in the 5-membered ring via the specified carbon atom, or via A_1 when A_1 is carbon; Q8 is linked toT via either of the specified carbon atoms in the 5-membered ring, and linked in the benzo-ring via either of the two specified carbon atoms on either side of the linking bond shown; and Q9 is linked via either of the two specified carbon atoms on either side of the linking bond shown;

wherein T is selected from the groups in (TA) to (TD) below (wherein AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are defined hereinbelow);

(TA) T is selected from the following groups :-

(TAa) AR1, AR1-(1-4C)alkyl-, AR2 (carbon linked), AR3;

(TAb) AR1-CH(OH), AR2-CH(OH)-, AR3-CH(OH)-;

(TAc) AR1-CO-, AR2-CO-, AR3-CO-, AR4-CO-;

(TAd) AR1-O-, AR2-O-, AR3-O-;

(TAe) AR1-S(O)q- , AR2-S(O)q- , AR3-S(O)q- (q is 0, 1 or 2);

(TAf) an optionally substituted N-linked (fully unsaturated) 5-membered heteroaryl ring system containing 1, 2 or 3 nitrogen atoms;

(TAg) a carbon linked tropol-3-one or tropol-4-one, optionally substituted in a position not adjacent to the linking position; or

(TB) T is selected from the following groups :-

(TBa) halo or (1-4C)alkyl

{optionally substituted by one or more groups each independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkanoyl, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, -NRvRw, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)q- (q is 0, 1 or 2), CY1, CY2 or AR1};

(TBb) -NRv'Rw' ;

(TBc) ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl;

(TBd) R^{10}CO- , $R^{10}S(O)_q$- (q is 0, 1 or 2) or R^{10}CS-

wherein R^{10} is selected from the following groups :-

(TBda) CY1 or CY2;

(TBdb) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, -NRvRw, ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl or 2-(AR2)ethenyl; or

(TBdc) (1-4C)alkyl {optionally substituted as defined in (TBa) above, or by (1-4C)alkylS(O)pNH- or (1-4C)alkylS(O)p-((1-4C)alkyl)N- (p is 1 or 2)};

wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl; Rv' is hydrogen, (1-4C)alkyl or (3-8C)cycloalkyl; Rw' is hydrogen, (1-4C)alkyl, (3-8C)cycloalkyl, (1-4C)alkyl-CO- or (1-4C)alkylS(O)q- (q is 1 or 2); or

(TC) T is selected from the following groups :-

(TCa) an optionally substituted, fully saturated 4-membered monocyclic ring containing 1

heteroatom selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or sp^3 carbon atom;

(TCb) an optionally substituted 5-membered monocyclic ring containing 1 heteroatom selected from O, N and S (optionally oxidised), and linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom, which monocyclic ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(TCc) an optionally substituted 6- or 7-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom, which monocyclic ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom; or

(TD) . T is selected from the following groups :-

(TDa) a bicyclic spiro-ring system containing 0, 1 or 2 ring nitrogen atoms as the only ring heteroatoms, the structure consisting of a 5- or 6-membered ring system (linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom) substituted (but not adjacent to the linking position) by a 3-, 4- or 5-membered spiro-carbon-linked ring; which bicyclic ring system is

(i) fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(ii) contains one -N(Rc)- group in the ring system (at least two carbon atoms away from the linking position when the link is via a nitrogen atom or an sp^2 carbon atom) or one -N(Rc)- group in an optional substituent (not adjacent to the linking position) and is

(iii) optionally further substituted on an available ring carbon atom; or

(TDb) a 7-, 8- or 9-membered bicyclic ring system (linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom) containing 0, 1 or 2 ring nitrogen atoms (and optionally a further O or S ring heteroatom), the structure containing a bridge of 1, 2 or 3 carbon atoms; which bicyclic ring system is

(i) fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(ii) contains one O or S heteroatom, or one -N(Rc)- group in the ring (at least two carbon atoms away from the linking position when the link is via a nitrogen atom or an sp^2 carbon atom) or one -N(Rc)- group in an optional substituent (not adjacent to the linking position) and is

(iii) optionally further substituted on an available ring carbon atom;

wherein Rc is selected from groups (Rc1) to (Rc5) :-

(Rc1) (1-6C)alkyl {optionally substituted by one or more (1-4C)alkanoyl groups (including geminal disubstitution) and/or optionally monosubstituted by cyano, (1-4C)alkoxy, trifluoromethyl, (1-4C)alkoxycarbonyl, phenyl (optionally substituted as for AR defined hereinafter), (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2); or, on any but the first carbon atom of the (1-6C)alkyl chain, optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy and fluoro, and/or optionally monosubstituted by oxo, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)$_p$NH- or (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N- (p is 1 or 2)};

(Rc2) R^{13}CO- , $R^{13}SO_2$- or R^{13}CS-

wherein R^{13} is selected from (Rc2a) to (Rc2e) :-

(Rc2a) AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;

(Rc2b) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl,
2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, 2-(AR2a)ethenyl;

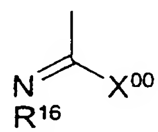
(Rc2c) (1-10C)alkyl
{optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkanoyl, phosphoryl [-O-P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from phosphonate [phosphono, -P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylaminocarbonyl, di((1-4C)alkyl)aminocarbonyl, (1-

4C)alkylS(O)p-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)pNH-, fluoro(1-4C)alkylS(O)p((1-4C)alkyl)N-, (1-4C)alkylS(O)q-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)q- , AR2-S(O)q- , AR3-S(O)q- , AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups};

(Rc2d) $R^{14}C(O)O$(1-6C)alkyl wherein R^{14} is AR1, AR2, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (Rc2c)};

(Rc2e) $R^{15}O$- wherein R^{15} is benzyl, (1-6C)alkyl {optionally substituted as defined for (Rc2c)}, CY1, CY2 or AR2b;

(Rc3) hydrogen, cyano, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, or of the formula **(Rc3a)**



(Rc3a)

wherein X^{00} is $-OR^{17}$, $-SR^{17}$, $-NHR^{17}$and $-N(R^{17})_2$;

wherein R^{17} is hydrogen (when X^{00} is $-NHR^{17}$and $-N(R^{17})_2$), and R^{17} is (1-4C)alkyl, phenyl or AR2 (when X^{00} is $-OR^{17}$, $-SR^{17}$ and $-NHR^{17}$); and R^{16} is cyano, nitro, (1-4C)alkylsulfonyl, (4-7C)cycloalkylsulfonyl, phenylsulfonyl, (1-4C)alkanoyl and (1-4C)alkoxycarbonyl;

(Rc4) trityl, AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b;

(Rc5) RdOC(Re)=CH(C=O)-, RfC(=O)C(=O)-, RgN=C(Rh)C(=O)- or RiNHC(Rj)=CHC(=O)- wherein Rd is (1-6C)alkyl; Re is hydrogen or (1-6C)alkyl, or Rd and Re together form a (3-4C)alkylene chain; Rf is hydrogen, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkyl, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-4C)alkylamino(2-6C)alkoxy, di-(1-4C)alkylamino(2-6C)alkoxy; Rg is (1-6C)alkyl, hydroxy or (1-6C)alkoxy; Rh is hydrogen or (1-6C)alkyl; Ri is hydrogen, (1-6C)alkyl, AR1, AR2, AR2a, AR2b and Rj is hydrogen or (1-6C)alkyl;

wherein

AR1 is an optionally substituted phenyl or optionally substituted naphthyl;

AR2 is an optionally substituted 5- or 6-membered, fully unsaturated (i.e with the maximum degree of unsaturation) monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

AR2a is a partially hydrogenated version of AR2 (i.e. AR2 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

AR2b is a fully hydrogenated version of AR2 (i.e. AR2 systems having no unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom;

AR3 is an optionally substituted 8-, 9- or 10-membered, fully unsaturated (i.e with the maximum degree of unsaturation) bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

AR3a is a partially hydrogenated version of AR3 (i.e. AR3 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;

AR3b is a fully hydrogenated version of AR3 (i.e. AR3 systems having no unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;

AR4 is an optionally substituted 13- or 14-membered, fully unsaturated (i.e with the maximum degree of unsaturation) tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in any of the rings comprising the tricyclic system;

AR4a is a partially hydrogenated version of AR4 (i.e. AR4 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

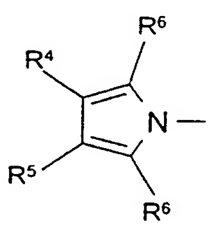
CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring.

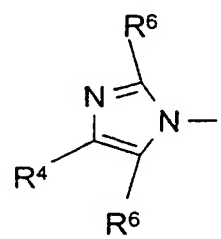
In this specification, where it is stated that a ring may be linked via an sp^2 carbon atom, which ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom, it is to be understood that the ring is linked via a C=C double bond.

In another emdodiment, (Rc1) is as defined above other than the optional phenyl substituent on (1-6C)alkyl is optionally substituted as for AR1 defined hereinafter; and (Rc2c), is as defined above and further includes carboxy as an optional substituent on R^{13} as (1-10C)alkyl.

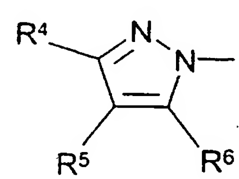
(TAf) When T is an optionally substituted N-linked (fully unsaturated) 5-membered heteroaryl ring system containing 1, 2 or 3 nitrogen atoms, it is preferably selected from a group of formula (TAf1) to (TAf6) below (particularly (TAf1), (TAf2), (TAf4) and (TAf5), and especially (TAf1) and/or (TAf2)). The above preferred values of (TAf) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.



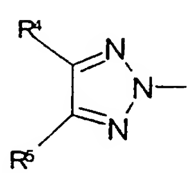
(TAf1)



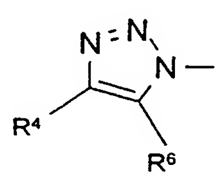
(TAf2)



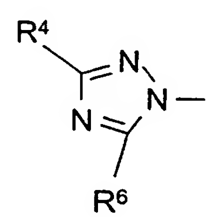
(TAf3)



(TAf4)



(TAf5)



(TAf6)

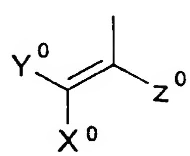
wherein :

R^6 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, carbamoyl and cyano;

R^4 and R^5 are independently selected from hydrogen, halo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)q- (q is 0, 1 or 2), (1-4C)alkanoyl, (1-4C)alkoxycarbonyl, (2-4C)alkanoyloxy-(1-4C)alkyl, benzoxy-(1-4C)alkyl, (2-4C)alkanoylamino, -CONRvRw, -NRvRw and (1-4C)alkyl {optionally substituted by hydroxy, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)q- (q is 0, 1 or 2), (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw, -NRvRw; wherein RvRw is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl};

or R^4 is selected from one of the groups in (TAfa) to (TAfc) below, or (where appropriate) one of R^4 and R^5 is selected from the above list of R^4 and R^5 values, and the other is selected from one of the groups in (TAfa) to (TAfc) below :-

(TAfa) a group of the formula (TAfa1)



(TAfa1)

wherein Z^0 is hydrogen or (1-4C)alkyl;

X^0 and Y^0 are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, halo, cyano, nitro, (1-4C)alkylS(O)q- (q is 0, 1 or 2), $RvRwNSO_2$-, trifluoromethyl, pentafluoroethyl, (1-4C)alkanoyl and -CONRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]; or

one of X^0 and Y^0 is selected from the above list of X^0 and Y^0 values, and the other is selected from phenyl, phenylcarbonyl, $-S(O)_q$-phenyl (q is 0, 1 or 2), N-(phenyl)carbamoyl, phenylaminosulfonyl, AR2, (AR2)-CO-, (AR2)-S(O)q- (q is 0, 1 or 2), N-(AR2)carbamoyl and (AR2)aminosulfonyl; wherein any phenyl group in (TAfa) may be optionally substituted by up to three substituents independently selected from (1-4C)alkyl, cyano, trifluoromethyl, nitro, halo and (1-4C)alkylsulfonyl;

(TAfb) an acetylene of the formula -≡-H or -≡-(1-4C)alkyl;

(TAfc) $-X^1-Y^1$-AR2, $-X^1-Y^1$-AR2a, $-X^1-Y^1$-AR2b, $-X^1-Y^1$-AR3, $-X^1-Y^1$-AR3a or $-X^1-Y^1$-AR3b;

wherein X^1 is a direct bond or -CH(OH)- and

Y^1 is $-(CH_2)_m-$, $-(CH_2)_n-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$ or $-C(=O)O-(CH_2)_m-$;

or wherein X^1 is $-(CH_2)_n-$ or $-CH(Me)-(CH_2)_m-$ and

Y^1 is $-(CH_2)_m-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$, $-C(=O)O-(CH_2)_m-$ or $-S(O)_q-(CH_2)_m-$;

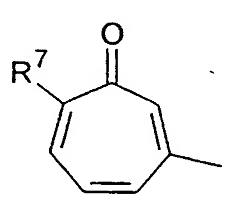
or wherein X^1 is $-CH_2O-$, $-CH_2NH-$ or $-CH_2N((1\text{-}4C)alkyl)-$ and

Y^1 is $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$ or $-C(=S)NH-(CH_2)_m-$; and additionally Y^1 is $-SO_2-$ when X^1 is $-CH_2NH-$ or $-CH_2N((1\text{-}4C)alkyl)-$, and Y^1 is $-(CH_2)_m-$ when X^1 is $-CH_2O-$ or $-CH_2N((1\text{-}4C)alkyl)-$; wherein n is 1, 2 or 3; m is 0, 1, 2 or 3 and q is 0, 1 or 2; and when Y^1 is $-(CH_2)_m-NH-(CH_2)_m-$ each m is independently selected from 0, 1, 2 or 3.

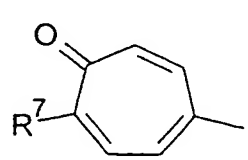
It is to be understood that when a value for $-X^1-$ is a two-atom link and is written, for example, as $-CH_2NH-$ it is the left hand part ($-CH_2-$ here) which is bonded to the group of formula (TAf1) to (TAf6) and the right hand part (-NH- here) which is bonded to $-Y^1-$ in the definition in (TAfc). Similarly, when $-Y^1-$ is a two-atom link and is written, for example, as -CONH- it is the left hand part of $-Y^1-$ (-CO- here) which is bonded to the right hand part of $-X^1-$, and the right hand part of $-Y^1-$ (-NH- here) which is bonded to the AR2, AR2a, AR2b, AR3, AR3a or AR3b moiety in the definition in (TAfc).

Preferably R^6 is hydrogen or (1-4C)alkyl, and R^4 and R^5 are independently selected from hydrogen, (1-4C)alkyl or one of R^4 and R^5 is selected from group (TAfa). Other preferable substituents on the (TAf1) to (TAf6) are illustrated in the accompanying Examples.

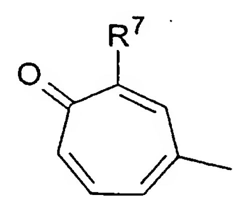
(TAg) When T is a carbon linked tropol-3-one or tropol-4-one, optionally substituted in a position not adjacent to the linking position **(TAg)**, it is preferably selected from a group of formula (TAg1), (TAg2) or (TAg3). The above preferred values of (TAg) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.



(TAg1)



(TAg2)



(TAg3)

wherein R^7 is selected from

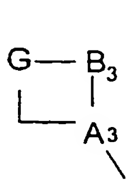
(TAga) hydrogen, (1-4C)alkyl {optionally substituted by one or two substituents (excluding geminal disubstitution) independently selected from fluoro, hydroxy, (1-4C)alkoxy and -NRvRw]}; or

(TAgb) R^8-O-, R^8-S-, R^8-NH- or R^8R^8-N-;

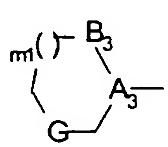
wherein R^8 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl or (3-8C)cycloalkyl {both optionally substituted by one or two substituents (excluding geminal disubstitution) independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and -NRvRw}, (2-4C)alkenyl {optionally substituted by one or two -NRvRw substituents}, (1-4C)alkanoyl {optionally substituted by one or two substituents independently selected from -NRvRw and hydroxy}, phenyl-(1-4C)alkyl or pyridyl-(1-4C)alkyl {the phenyl and pyridyl (preferably pyridin-4-yl) rings being optionally substituted by one or two -NRvRw substituents}; or

(TAgc) morpholino, thiomorpholino, pyrrolidino {optionally independently substituted in the 3- and/or 4-positions by (1-4C)alkyl}, piperidino substituted in the 4-position by R^9-, R^9-O-, R^9-S-, R^9-NH- or R^9R^9-N-; wherein R^9 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl {optionally substituted by one or two (excluding geminal disubstitution) hydroxy, (1-4C)alkoxy, (1-4C)alkoxycarbonyl or -NRvRw} and piperazino {optionally substituted in the 4-position by (1-4C)alkyl, (3-8C)cycloalkyl, (1-4C)alkanoyl, (1-4C)alkoxycarbonyl or (1-4C)alkylsulfonyl, and optionally independently substituted in the 3- and/or 5-positions by (1-4C)alkyl}; wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl.

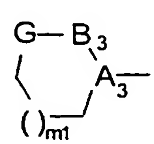
(TC) Preferred values for the optional substituents and groups defined in (TCa) to (TCc) are defined by formulae (TC1) to (TC4) :-



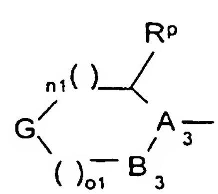
(TC1)



(TC2)



(TC3)



(TC4)

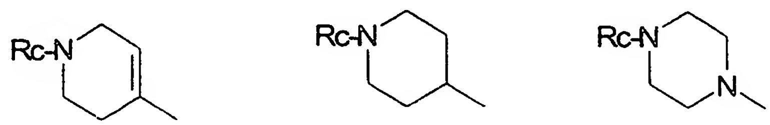
wherein in (TC1) : >A_3-B_3- is >C(Rq)-CH(Rr)- and G is -O-, -S-, -SO-, -SO_2- or >N(Rc);
wherein in (TC2) : m1 is 0, 1 or 2; >A_3-B_3- is >C=C(Rr)- or >C(Rq)-CH(Rr)- and G is -O-, -S-, -SO-, -SO_2- or >N(Rc);
wherein in (TC3) : m1 is 0, 1 or 2; >A_3-B_3- is >C(Rq)-CH(Rr)- (other than when Rq and Rr are both together hydrogen) and G is -O-, -S-, -SO-, -SO_2- or >N(Rc);
wherein in (TC4) : n1 is 1 or 2; o1 is 1 or 2 and n1 + o1 = 2 or 3; >A_3-B_3- is >C=C(Rr)- or >C(Rq)-CH(Rr)- or >N-CH_2- and G is -O-, -S-, -SO-, -SO_2- or >N(Rc); Rp is hydrogen, (1-4C)alkyl (other than when such substitution is defined by >A_3-B_3-), hydroxy, (1-4C)alkoxy or (1-4C)alkanoyloxy;
wherein in (TC1), (TC2) and (TC4); m1, n1 and o1 are as defined hereinbefore : >A_3-B_3- is >N-CH_2- and G is >C(R^{11})(R^{12}), >C=O, >C-OH, >C-(1-4C)alkoxy, >C=N-OH, >C=N-(1-4C)alkoxy, >C=N-NH-(1-4C)alkyl, >C=N-N((1-4C)alkyl)$_2$ (the last two (1-4C)alkyl groups above in G being optionally substituted by hydroxy) or >C=N-N-CO-(1-4C)alkoxy; wherein > represents two single bonds;
Rq is hydrogen, hydroxy, halo, (1-4C)alkyl or (1-4C)alkanoyloxy;
Rr is (independently where appropriate) hydrogen or (1-4C)alkyl;
R^{11} is hydrogen, (1-4C)alkyl, fluoro(1-4C)alkyl, (1-4C)alkyl-thio-(1-4C)alkyl or hydroxy-(1-4C)alkyl and R^{12} is -[C(Rr)(Rr)]$_{m2}$-N(Rr)(Rc) wherein m2 is 0, 1 or 2;
and, other than the ring substitution defined by G, >A_3-B_3- and Rp, each ring system may be optionally further substituted on a carbon atom not adjacent to the link at >A_3- by up to two substituents independently selected from (1-4C)alkyl, fluoro(1-4C)alkyl (including trifluoromethyl), (1-4C)alkyl-thio-(1-4C)alkyl, hydroxy-(1-4C)alkyl, amino, amino-(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR-oxymethyl, AR-thiomethyl, oxo (=O) (other than when G is >N-Rc and Rc is group **(Rc2)** defined hereinbefore) or independently selected from Rc; and also hydroxy or halo (the last two optional substituents only when G is -O- or -S-);
wherein AR is as defined for formula (IP) hereinafter; Rc is selected from groups (Rc1) to (Rc5) defined hereinbefore.

For the avoidance of doubt, $( )_{m1}$, $( )_{n1}$ and $( )_{o1}$ indicate (-CH_2-)$_{m1}$, (-CH_2-)$_{n1}$ and (-CH_2-)$_{o1}$ respectively (optionally substituted as described above).

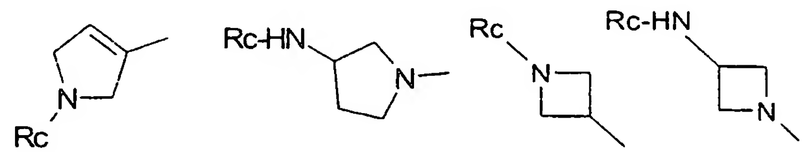
In the above definition of (TC1) to (TC4) and of the further optional substituents, AR

is preferably AR2, and the further optional substituents are preferably not selected from the values listed for Rc. A preferred value for G is >N(Rc) or >C(R^{11})(R^{12}).

Particularly preferred values for the optional substituents and groups defined in (TCa) to (TCc), and (TC1) to (TC4) are contained in the following definitions (TC5) to (TC11) :-



(TC5) (TC6) (TC7)



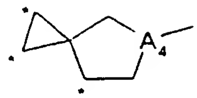
(TC8) (TC9) (TC10) (TC11)

wherein Rc has any of the values listed hereinbefore or hereinafter.

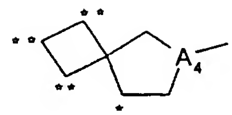
Especially preferred are (TC5), (TC6), (TC7) and (TC9), most especially (TC5) in which Rc has any of the values listed hereinbefore or hereinafter (especially R^{13}CO- with the preferable R^{13} values given hereinafter). In (TC5) Rc is preferably selected from the group (Rc2), especially R^{13}CO- with the preferable R^{13} values given hereinafter. In (TC7) Rc is preferably selected from group (Rc3) or (Rc4).

The above preferred values of (TCa) to (TCc) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O- (especially when HET is isoxazole).

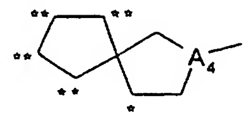
(TDa) When T is a bicyclic spiro-ring system as defined in (TDa), it is preferably selected from a group of formula (TDa1) to (TDa9). The above preferred values of (TDa) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.



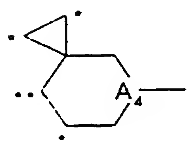
(TDa1)



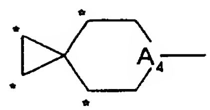
(TDa2)



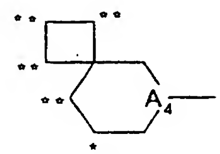
(TDa3)



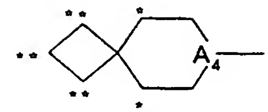
(TDa4)



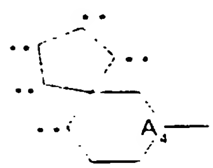
(TDa5)



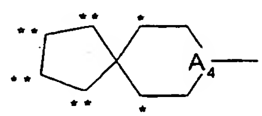
(TDa6)



(TDa7)



(TDa8)



(TDa9)

wherein;

(i) the A_4 linking group is a nitrogen atom or an sp^3 or sp^2 carbon atom (with the double bond, where appropriate, orientated in either direction); and

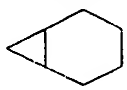
(ii) one of the ring carbon atoms at positions marked * and ** is replaced by one of the following groups -NRc-, >CH-NHRc, >CH-NRc-(1-4C)alkyl, >CH-CH_2-NHRc, >CH-CH_2-NRc-(1-4C)alkyl [wherein a central -CH_2- chain link is optionally mono- or di-substituted by (1-4C)alkyl]; with the provisos that positions marked * are not replaced by -NH- in the ring containing the A_4 link when A_4 is a nitrogen atom or an sp^2 carbon atom, and that positions marked * are not replaced by -NH- in the three membered ring in (TDa1), (TDa4) and (TDa5); and

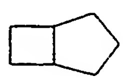
(iii) the ring system is optionally (further) substituted on an available ring carbon atom by up to two substituents independently selected from (1-4C)alkyl, fluoro(1-4C)alkyl (including trifluoromethyl), (1-4C)alkyl-thio-(1-4C)alkyl, hydroxy-(1-4C)alkyl, amino, amino-(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR2-oxymethyl, AR2-thiomethyl, oxo (=O) (other than when the ring contains an >N-Rc and Rc is group (Rc2)) and also hydroxy or halo;

wherein Rc has any of the values listed hereinbefore or hereinafter.

(TDb) When T is a 7-, 8- or 9-membered bicyclic ring system containing a bridge of 1, 2 or 3 carbon atoms as defined in (TDb), it is preferably selected from a group defined by the ring skeletons shown in formulae (TDb1) to (TDb14) :-

7-membered ring skeletons


[4,1,0]
(TDb1)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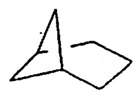
(TDb2)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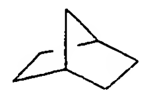
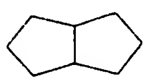
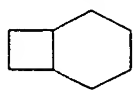
(TDb3)

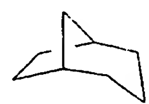

[2,2,1]
(TDb4)

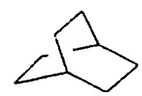
8-membered ring skeletons


[3,3,0]
(TDb5)

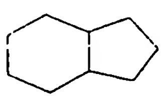

[4,2,0]
(TDb6)

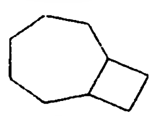

[4,1,1]
(TDb7)


[3,2,1]
(TDb8)

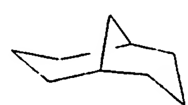

[2,2,2]
(TDb9)

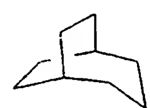
9-membered ring skeletons


[4,3,0]
(TDb10)


[5,2,0]
(TDb11)


[4,2,1]
(TDb12)


[3,3,1]
(TDb13)


[3,2,2]
(TDb14)

wherein;

(i) the ring system contains 0, 1 or 2 ring nitrogen atoms (and optionally a further O or S ring heteroatom),and when present the ring nitrogen, O or S heteroatom/s are at any position other than as part of the 3-membered ring in (TDb1);

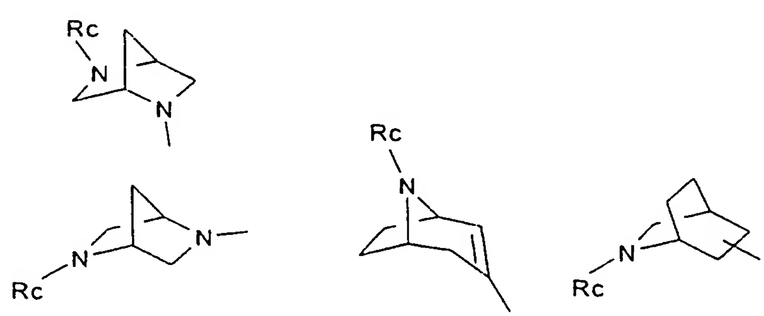
(ii) the ring system is linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom (with the double bond, where appropriate, orientated in either direction) from any position in either ring [other than from a bridgehead position or from an sp^2 carbon atom in the 4-membered ring in (TDb2), (TDb6) and (TDb11)];

(iii) one of the ring carbon atoms at a position not adjacent to the linking position, is replaced (other than when the ring contains an O or S heteroatom) by one of the following groups -NRc- [not at a bridgehead position], >C(H)-NHRc, >C(H)-NRc-(1-4C)alkyl, >C(H)-CH_2-NHRc, >C(H)-CH_2-NRc-(1-4C)alkyl [wherein the hydrogen atom shown in brackets is not present when the replacement is made at a bridgehead position and wherein a central -CH_2- chain link is optionally mono- or di-substituted by (1-4C)alkyl]; with the proviso that when the ring system is linked via a ring nitrogen atom or an sp^2 carbon atom any replacement of a ring carbon atom by -NRc-, O or S is at least two carbon atoms away from the linking position; and

(iv) the ring system is optionally (further) substituted on an available ring carbon atom as for the bicyclic spiro-ring systems described in (TDa); wherein Rc has any of the values listed hereinbefore or hereinafter.

It will be appreciated that unstable anti-Bredt compounds are not contemplated in this definition (i.e. compounds with stuctures (TDb3), (TDb4), (TDb7), (TDb8), (TDb9), (TDb12), (TDb13) and (TDb14) in which an sp^2 carbon atom is directed towards a bridgehead position).

Particularly preferred values of (TDb) are the following structures of formula (TDb4), (TDb8) and/or (TDb9); wherein Rc has any of the values listed hereinbefore or hereinafter. The above preferred values of (TDb) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.

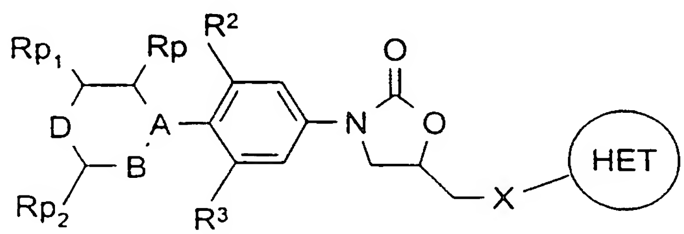


[2,2,1] (TDb4a & b) [3,2,1] (TDb8) [2,2,2] (TDb9)

In another embodiment there is provided a compound of the formula (I) which is defined by the formula (IP) below, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein

X is -O-, -S-, -SO- or -SO_2-;

HET is a C-linked 5-membered heteroaryl ring containing 2 or 3 heteroatoms independently selected from N, O and S (with the proviso that there are no O-O, O-S or S-S bonds), which ring is optionally substituted on any available C atom (provided that when a N atom is adjacent to the X-link, there is no substitution on any C atom that is adjacent to this N atom) by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available N atom (provided that the ring is not thereby quaternised), by (1-4C)alkyl;



(IP)

wherein: R^2 and R^3 are independently hydrogen or fluoro;

Rp is hydrogen, (1-4C)alkyl, hydroxy, (1-4C)alkoxy or (2-4C)alkanoyloxy;

>A-B- is of the formula >C=C(Rr)- , >CHCHRr- , >C(OH)CHRr- or >N-CH_2-

(> represents two single bonds) wherein Rr is hydrogen or (1-4C)alkyl;

D is -O-, -S-, -SO-, -SO_2- or >NRcp;

Rp1 and Rp2 are independently oxo (=O) [but not when Rcp is group **(PC)** below], (1-4C)alkyl, (1-4C)alkanoylamino-(1-4C)alkyl, hydroxy-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR-oxymethyl, AR-thiomethyl (wherein AR is as defined hereinbelow) or independently as defined for Rcp hereinbelow with the proviso that Rp1 and Rp2 are not phenyl, benzyl, AR (as defined hereinbelow), a tetrazole ring system, cyclopentyl or cyclohexyl; and when D is -O- or -S-, Rp1 and Rp2 are additionally independently hydroxy or bromo;

wherein Rcp is selected from (PA) to (PE) below :-

(PA) hydrogen, cyano, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl;

(PB) phenyl, benzyl, AR (as defined hereinbelow) or a tetrazole ring system [optionally mono-substituted in the 1- or 2- position of the tetrazole ring by (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl or (1-4C)alkanoyl] wherein the tetrazole ring system is joined to the nitrogen in

>NRcp by a ring carbon atom;

(PC) R^{13p}CO- , $R^{13p}SO_2$- or R^{13p}CS- wherein R^{13p} is selected from (PCa) to (PCf) :-

(PCa) AR (as defined hereinbelow);

(PCb) cyclopentyl or cyclohexyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl or 1,4-dioxan-2-yl [optionally mono- or di-substituted by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), hydroxy (but excluding 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl or 1,4-dioxan-2-yl substituted by hydroxy), (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano and trifluoromethyl];

(PCc) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, amino, (1-4C)alkylamino, di((1-4C)alkyl)amino, 2-(5- or 6-membered heteroaryl)ethenyl, 2-(5- or 6-membered (partially) hydrogenated heteroaryl)ethenyl, 2-phenylethenyl [wherein the heteroaryl or phenyl substituent is optionally substituted on an available carbon atom by up to three substituents independently selected from (1-4C)alkoxy, halo, cyano and (for the phenyl substituent only) (1-4C)alkylsulfonyl];

(PCd) (1-10C)alkyl [optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy and amino, or optionally monosubstituted by cyano, halo, (1-10C)alkoxy, trifluoromethyl, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(2-6C)alkanoylamino, (1-4C)alkylS(O)$_p$NH-, (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)$_p$NH-, fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-, phosphono, (1-4C)alkoxy(hydroxy)phosphoryl, di-(1-4C)alkoxyphosphoryl, (1-4C)alkylS(O)$_q$-, phenyl, naphthyl, phenoxy, naphthoxy, phenylamino, naphthylamino, phenylS(O)$_q$-, naphthylS(O)$_q$- [wherein said phenyl and naphthyl groups are optionally substituted by up to three substituents independently selected from (1-4C)alkoxy, halo and cyano], or CY (as defined hereinbelow), wherein p is 1 or 2 and q is 0, 1 or 2];

(PCe) R^{14p}C(O)O(1-6C)alkyl wherein R^{14p} is an optionally substituted 5- or 6-membered heteroaryl, optionally substituted phenyl, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or optionally substituted (1-10C)alkyl;

(PCf) R^{15p}O- wherein R^{15p} is benzyl or optionally substituted (1-6C)alkyl;

(PD) RdOC(Re)=CH(C=O)-, RfC(=O)C(=O)-, RgN=C(Rh)C(=O)- or RiNHC(Rj)=CHC(=O)- wherein Rd is (1-6C)alkyl; Re is hydrogen or (1-6C)alkyl, or Rd and Re together form a (3-4C)alkylene chain; Rf is hydrogen, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkyl, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-4C)alkylamino(2-6C)alkoxy, di-(1-4C)alkylamino(2-6C)alkoxy; Rg is (1-6C)alkyl, hydroxy or (1-6C)alkoxy; Rh is hydrogen or (1-6C)alkyl; Ri is hydrogen, (1-6C)alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heteroaryl [and (partially) hydrogenated versions thereof] and Rj is hydrogen or (1-6C)alkyl;

(PE) $R^{16p}CH(R^{17p})(CH_2)_{mp}$- wherein mp is 0 or 1; R^{17p} is fluoro, cyano, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkoxycarbonyl or hydroxy, (provided that when mp is 0, R^{17p} is not fluoro or hydroxy) and R^{16p} is hydrogen or (1-4C)alkyl;

wherein AR is optionally substituted phenyl, optionally substituted phenyl(1-4C)alkyl, optionally substituted naphthyl, optionally substituted 5- or 6-membered heteroaryl;

wherein AR is also an optionally substituted 5/6 or 6/6 bicyclic heteroaryl ring system, in which the bicyclic heteroaryl ring systems may be linked via an atom in either of the rings comprising the bicyclic system, and wherein both the mono- and bicyclic heteroaryl ring systems are linked via a ring carbon atom and may be (partially) hydrogenated;

wherein CY is selected from :-

(i) cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl or cyclohexenyl ring;

(ii) 5- or 6-membered heteroaryl, 5- or 6-membered heteroaryloxy, 5- or 6-membered heteroaryl-$S(O)_q$-, 5- or 6-membered heteroarylamino [and (partially) hydrogenated versions thereof] and

(iii) 5/6 or 6/6 bicyclic heteroaryl, 5/6 or 6/6 bicyclic heteroaryloxy, 5/6 or 6/6 bicyclic heteroaryl-$S(O)_q$-, 5/6 or 6/6 bicyclic heteroarylamino [and (partially) hydrogenated versions thereof]; wherein q is 0, 1 or 2 and any of the afore-mentioned ring systems in CY may be optionally substituted by up to three substituents independently selected from halo, (1-4C)alkyl [including geminal disubstitution when CY is a cycloalkyl or cycloalkenyl ring in (i)], acyl, oxo and nitro-(1-4C)alkyl.

For the avoidance of doubt, phosphono is $-P(O)(OH)_2$; (1-4C)alkoxy(hydroxy)-phosphoryl is a mono-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$; and di-(1-

4C)alkoxyphosphoryl is a di-(1-4C)alkoxy derivative of -O-P(O)$(OH)_2$.

In this embodiment of formula (IP) a '5- or 6-membered heteroaryl' and 'heteroaryl (monocyclic) ring' means a 5- or 6-membered aryl ring wherein (unless stated otherwise) 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen and sulfur. Unless stated otherwise, such rings are fully aromatic. Particular examples of 5- or 6-membered heteroaryl ring systems are furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene.

Particular examples of 5-membered heteroaryl rings containing 2 or 3 heteroatoms independently selected from N, O and S (with the proviso that there are no O-O, O-S or S-S bonds; and in an alternative embodiment, also no N-S bonds) are pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole; and also in an alternative embodiment, isothiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole or 1,2,3-thiadiazole.

In this embodiment of formula (IP) a '5/6 or 6/6 bicyclic heteroaryl ring system' and 'heteroaryl (bicyclic) ring' means an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring, the bicyclic ring system containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise, such rings are fully aromatic. Particular examples of 5/6 and 6/6 bicyclic ring systems are indole, benzofuran, benzimidazole, benzothiophene, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine.

Particular optional substituents for alkyl, phenyl (and phenyl containing moieties) and naphthyl groups and ring carbon atoms in heteroaryl (mono or bicyclic) rings in R^{14p}, R^{15p}, Ri and AR include halo, (1-4C)alkyl , hydroxy, nitro, carbamoyl, (1-4C)alkylcarbamoyl, di-((1-4C)alkyl)carbamoyl, cyano, trifluoromethyl, trifluoromethoxy, amino, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-4C)alkyl $S(O)_q$- (q is 0, 1 or 2), carboxy, (1-4C)alkoxycarbonyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkanoyl, (1-4C)alkoxy, (1-4C)alkyl$S(O)_2$amino, (1-4C)alkanoylamino, benzoylamino, benzoyl, phenyl (optionally substituted by up to three substituents selected from halo, (1-4C)alkoxy or cyano), furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, hydroxy-(1-4C)alkyl, halo-(1-

4C)alkyl, nitro(1-4C)alkyl, amino(1-4C)alkyl, cyano(1-4C)alkyl, (1-4C)alkanesulfonamido, aminosulfonyl, (1-4C)alkylaminosulfonyl and di-((1-4C)alkyl)aminosulfonyl. The phenyl and naphthyl groups and heteroaryl (mono- or bicyclic) rings in R^{14p}, Ri and AR may be mono- or di-substituted on ring carbon atoms with substituents independently selected from the above list of particular optional substituents.

In this specification the term 'alkyl' includes straight chained and branched structures. For example, (1-6C)alkyl includes propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. A similar convention applies to other radicals, for example halo(1-4C)alkyl includes 1-bromoethyl and 2-bromoethyl.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter.

Examples of **(1-4C)alkyl** and **(1-5C)alkyl** include methyl, ethyl, and propyl and isopropyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl and hexyl; examples of **(1-10C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl and nonyl; examples of **(1-4C)alkanoylamino-(1-4C)alkyl** include formamidomethyl, acetamidomethyl and acetamidoethyl; examples of **hydroxy(1-4C)alkyl** and **hydroxy(1-6C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **2-((1-4C)alkoxycarbonyl)ethenyl** include 2-(methoxycarbonyl)ethenyl and 2-(ethoxycarbonyl)ethenyl; examples of **2-cyano-2-((1-4C)alkyl)ethenyl** include 2-cyano-2-methylethenyl and 2-cyano-2-ethylethenyl; examples of **2-nitro-2-((1-4C)alkyl)ethenyl** include 2-nitro-2-methylethenyl and 2-nitro-2-ethylethenyl; examples of **2-((1-4C)alkylaminocarbonyl)ethenyl** include 2-(methylaminocarbonyl)ethenyl and 2-(ethylaminocarbonyl)ethenyl; examples of **(2-4C)alkenyl** include allyl and vinyl; examples of **(2-4C)alkynyl** include ethynyl and 2-propynyl; examples of **(1-4C)alkanoyl** include formyl, acetyl and propionyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-6C)alkoxy** and **(1-10C)alkoxy** include methoxy, ethoxy, propoxy and pentoxy; examples of **(1-4C)alkylthio**

include methylthio and ethylthio; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-4C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and dipropylamino; examples of **halo** groups include fluoro, chloro and bromo; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl and ethylsulfonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxy** and **(1-6C)alkoxy-(1-6C)alkoxy** include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of
(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy include 2-(methoxymethoxy)ethoxy, 2-(2-methoxyethoxy)ethoxy; 3-(2-methoxyethoxy)propoxy and 2-(2-ethoxyethoxy)ethoxy; examples of **(1-4C)alkylS(O)$_2$amino** include methylsulfonylamino and ethylsulfonylamino; examples of **(1-4C)alkanoylamino** and **(1-6C)alkanoylamino** include formamido, acetamido and propionylamino; examples of **(1-4C)alkoxycarbonylamino** include methoxycarbonylamino and ethoxycarbonylamino; examples of **N-(1-4C)alkyl-N-(1-6C)alkanoylamino** include N-methylacetamido, N-ethylacetamido and N-methylpropionamido; examples of **(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include methylsulfinylamino, methylsulfonylamino, ethylsulfinylamino and ethylsulfonylamino; examples of **(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-** wherein p is 1 or 2 include methylsulfinylmethylamino, methylsulfonylmethylamino, 2-(ethylsulfinyl)ethylamino and 2-(ethylsulfonyl)ethylamino; examples of **fluoro(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include trifluoromethylsulfinylamino and trifluoromethylsulfonylamino; examples of **fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)NH-** wherein p is 1 or 2 include trifluoromethylsulfinylmethylamino and trifluoromethylsulfonylmethylamino examples of **(1-4C)alkoxy(hydroxy)phosphoryl** include methoxy(hydroxy)phosphoryl and ethoxy(hydroxy)phosphoryl; examples of **di-(1-4C)alkoxyphosphoryl** include di-methoxyphosphoryl, di-ethoxyphosphoryl and ethoxy(methoxy)phosphoryl;
examples of **(1-4C)alkylS(O)$_q$-** wherein q is 0, 1 or 2 include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of **phenylS(O)$_q$** and **naphthylS(O)$_q$-** wherein q is 0, 1 or 2 are phenylthio, phenylsulfinyl, phenylsulfonyl and naphthylthio, naphthylsulfinyl and naphthylsulfonyl respectively; examples of **benzyloxy-(1-4C)alkyl** include benzyloxymethyl and benzyloxyethyl; examples of a **(3-4C)alkylene** chain are trimethylene or tetramethylene; examples of **(1-6C)alkoxy-(1-6C)alkyl** include

methoxymethyl, ethoxymethyl and 2-methoxyethyl; examples of **hydroxy-(2-6C)alkoxy** include 2-hydroxyethoxy and 3-hydroxypropoxy; examples of **(1-4C)alkylamino-(2-6C)alkoxy** include 2-methylaminoethoxy and 2-ethylaminoethoxy; examples of **di-(1-4C)alkylamino-(2-6C)alkoxy** include 2-dimethylaminoethoxy and 2-diethylaminoethoxy; examples of **phenyl(1-4C)alkyl** include benzyl and phenethyl; examples of **(1-4C)alkylcarbamoyl** include methylcarbamoyl and ethylcarbamoyl; examples of **di((1-4C)alkyl)carbamoyl** include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of **hydroxyimino(1-4C)alkyl** include hydroxyiminomethyl, 2-(hydroxyimino)ethyl and 1-(hydroxyimino)ethyl; examples of **(1-4C)alkoxyimino-(1-4C)alkyl** include methoxyiminomethyl, ethoxyiminomethyl, 1-(methoxyimino)ethyl and 2-(methoxyimino)ethyl; examples of **halo(1-4C)alkyl** include, halomethyl, 1-haloethyl, 2-haloethyl, and 3-halopropyl; examples of **nitro(1-4C)alkyl** include nitromethyl, 1-nitroethyl, 2-nitroethyl and 3-nitropropyl; examples of **amino(1-4C)alkyl** include aminomethyl, 1-aminoethyl, 2-aminoethyl and 3-aminopropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl; examples of **(1-4C)alkanesulfonamido** include methanesulfonamido and ethanesulfonamido; examples of **(1-4C)alkylaminosulfonyl** include methylaminosulfonyl and ethylaminosulfonyl; and examples of **di-(1-4C)alkylaminosulfonyl** include dimethylaminosulfonyl, diethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl; examples of **(1-4C)alkanesulfonyloxy** include methylsulfonyloxy, ethylsulfonyloxy and propylsulfonyloxy; examples of **(1-4C)alkanoyloxy** include acetoxy; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl and ethylaminocarbonyl; examples of **di((1-4C)alkyl)aminocarbonyl** include dimethylaminocarbonyl and diethylaminocarbonyl; examples of **(3-8C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(4-7C)cycloalkyl** include cyclobutyl, cyclopentyl and cyclohexyl; examples of **di(N-(1-4C)alkyl)aminomethylimino** include dimethylaminomethylimino and diethylaminomethylimino.

Particular values for AR2 include, for example, for those AR2 containing one heteroatom, furan, pyrrole, thiophene; for those AR2 containing one to four N atoms, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- & 1,2,4-triazole and tetrazole; for those AR2 containing one N and one O atom, oxazole, isoxazole and oxazine;

for those AR2 containing one N and one S atom, thiazole and isothiazole;
for those AR2 containing two N atoms and one S atom, 1,2,4- and 1,3,4-thiadiazole.

Particular examples of AR2a include, for example, dihydropyrrole (especially 2,5-dihydropyrrol-4-yl) and tetrahydropyridine (especially 1,2,5,6-tetrahydropyrid-4-yl).

Particular examples of AR2b include, for example, tetrahydrofuran, pyrrolidine, morpholine (preferably morpholino), thiomorpholine (preferably thiomorpholino), piperazine (preferably piperazino), imidazoline and piperidine, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Particular values for AR3 include, for example, bicyclic benzo-fused systems containing a 5- or 6-membered heteroaryl ring containing one nitrogen atom and optionally 1-3 further heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, indole, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzisothiazole, benzoxazole, benzisoxazole, quinoline, quinoxaline, quinazoline, phthalazine and cinnoline.

Other particular examples of AR3 include 5/5-, 5/6 and 6/6 bicyclic ring systems containing heteroatoms in both of the rings. Specific examples of such ring systems include, for example, purine and naphthyridine.

Further particular examples of AR3 include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, 3H-pyrrolo[1,2-a]pyrrole, pyrrolo[2,1-b]thiazole, 1H-imidazo[1,2-a]pyrrole, 1H-imidazo[1,2-a]imidazole, 1H,3H-pyrrolo[1,2-c]oxazole, 1H-imidazo[1,5-a]pyrrole, pyrrolo[1,2-b]isoxazole, imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, indolizine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrazine, pyrrolo[1,2-a]pyrimidine, pyrido[2,1-c]-s-triazole, s-triazole[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrazine, imidazo[1,5-a]pyrimidine, imidazo[1,2-b]-pyridazine, s-triazolo[4,3-a]pyrimidine, imidazo[5,1-b]oxazole and imidazo[2,1-b]oxazole. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazine, [3H]-oxazolo[3,4-a]pyridine, [6H]-pyrrolo[2,1-c]oxazine and pyrido[2,1-c][1,4]oxazine. Other

specific examples of 5/5- bicyclic ring systems are imidazooxazole or imidazothiazole, in particular imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole or imidazo[2,1-b]oxazole.

Particular examples of AR3a and AR3b include, for example, indoline, 1,3,4,6,9,9a-hexahydropyrido[2,1c][1,4]oxazin-8-yl, 1,2,3,5,8,8a-hexahydroimidazo[1,5a]pyridin-7-yl, 1,5,8,8a-tetrahydrooxazolo[3,4a]pyridin-7-yl, 1,5,6,7,8,8a-hexahydrooxazolo[3,4a]pyridin-7-yl, (7aS)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, (7aS)[5H]-1,2,3,7a-tetrahydropyrrolo[1,2c]imidazol-6-yl, (7aR)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, [3H,5H]-pyrrolo[1,2-c]oxazol-6-yl, [5H]-2,3-dihydropyrrolo[1,2-c]imidazol-6-yl, [3H,5H]-pyrrolo[1,2-c]thiazol-6-yl, [3H,5H]-1,7a-dihydropyrrolo[1,2-c]thiazol-6-yl, [5H]-pyrrolo[1,2-c]imidazol-6-yl, [1H]-3,4,8,8a-tetrahydropyrrolo[2,1-c]oxazin-7-yl, [3H]-1,5,8,8a-tetrahydrooxazolo[3,4-a]pyrid-7-yl, [3H]-5,8-dihydroxazolo[3,4-a]pyrid-7-yl and 5,8-dihydroimidazo[1,5-a]pyrid-7-yl.

Particular values for AR4 include, for example, pyrrolo[a]quinoline, 2,3-pyrroloisoquinoline, pyrrolo[a]isoquinoline, 1H-pyrrolo[1,2-a]benzimidazole, 9H-imidazo[1,2-a]indole, 5H-imidazo[2,1-a]isoindole, 1H-imidazo[3,4-a]indole, imidazo[1,2-a]quinoline, imidazo[2,1-a]isoquinoline, imidazo[1,5-a]quinoline and imidazo[5,1-a]isoquinoline.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen), W.L.Mosby (Intercsience Publishers Inc., New York), 1961, Parts 1 and 2.

Where optional substituents are listed such substitution is preferably not geminal disubstitution unless stated otherwise. If not stated elsewhere suitable optional substituents for a particular group are those as stated for similar groups herein.

Suitable substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are (on an available carbon atom) up to three substituents independently selected from (1-4C)alkyl {optionally substituted by (preferably one) substituents selected independently from hydroxy, trifluoromethyl, (1-4C)alkyl $S(O)_q$- (q is 0, 1 or 2) (this last substituent preferably on AR1 only), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, (1-4C)alkanoylamino, -CONRvRw or -NRvRw}, trifluoromethyl, hydroxy, halo, nitro, cyano,

thiol, (1-4C)alkoxy, (1-4C)alkanoyloxy, dimethylaminomethyleneaminocarbonyl, di(N-(1-4C)alkyl)aminomethylimino, carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, (1-4C)alkylSO$_2$amino, (2-4C)alkenyl {optionally substituted by carboxy or (1-4C)alkoxycarbonyl}, (2-4C)alkynyl, (1-4C)alkanoylamino, oxo (=O), thioxo (=S), (1-4C)alkanoylamino {the (1-4C)alkanoyl group being optionally substituted by hydroxy}, (1-4C)alkyl S(O)q- (q is 0, 1 or 2) {the (1-4C)alkyl group being optionally substituted by one or more groups independently selected from cyano, hydroxy and (1-4C)alkoxy}, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl].

Further suitable substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 (on an available carbon atom), and also on alkyl groups (unless indicated otherwise) are up to three substituents independently selected from trifluoromethoxy, benzoylamino, benzoyl, phenyl {optionally substituted by up to three substituents independently selected from halo, (1-4C)alkoxy or cyano}, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, halo-(1-4C)alkyl, (1-4C)alkanesulfonamido, -SO$_2$NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl].

Preferable optional substituents on Ar2b as 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl or 1,4-dioxan-2-yl are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, trifluoromethyl and phenyl].

Preferable optional substituents on CY1 & CY2 are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, and trifluoromethyl.

Suitable substituents on AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4 and AR4a are (on an available nitrogen atom, where such substitution does not result in quaternization) (1-4C)alkyl, (1-4C)alkanoyl {wherein the (1-4C)alkyl and (1-4C)alkanoyl groups are optionally substituted by (preferably one) substituents independently selected from cyano, hydroxy, nitro, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw or -NRvRw [wherein Rv is hydrogen

or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]}, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxycarbonyl or oxo (to form an N-oxide).

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

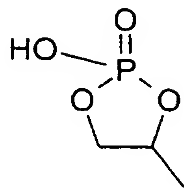
d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

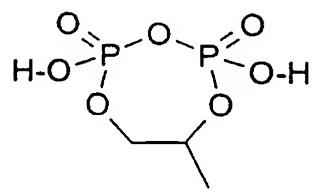
An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include chloromethyl or aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring.

Certain suitable in-vivo hydrolysable esters of a compound of the formula (I) are described within the definitions listed in this specification, for example esters described by the definition (Rc2d), and some groups within (Rc2c). Suitable in-vivo hydrolysable esters of a compound of the formula (I) are described as follows. For example, a 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a pyrophosphate of formula (PD2) :



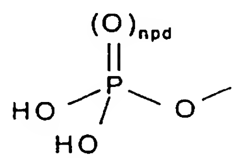
(PD1)



(PD2)

Particularly interesting are such cyclised pro-drugs when the 1,2-diol is on a (1-4C)alkyl chain linked to a carbonyl group in a substituent of formula Rc borne by a nitrogen atom in (TC4). Esters of compounds of formula (I) wherein the HO- function/s in (PD1) and (PD2) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of formula (I) in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD3) :



(PD3)

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD3) in which either or both of the -OH groups in (PD3) is independently protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2) and (PD3) may be prepared by reaction of a compound of formula (I) containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

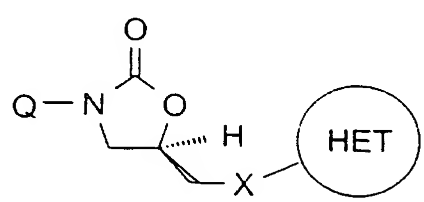
When a compound of formula (I) contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used

to selectively phosphorylate or dephosphorylate alcohol functionalities.

Other interesting in-vivo hydrolysable esters include, for example, those in which Rc is defined by, for example, $R^{14}C(O)O(1\text{-}6C)alkyl\text{-}CO\text{-}$ (wherein R^{14} is for example, benzyloxy-(1-4C)alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(1-4C)piperazino-(1-4C)alkyl, piperazino-(1-4C)alkyl and morpholino-(1-4C)alkyl.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2) and/or (PD3) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo hydrolysable ester prodrug of a compound of formula (I) contains two (PD3) groups, there are four HO-P- functionalities present in the overall molecule, each of which may form an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

The compounds of the present invention have a chiral centre at the C-5 position of the oxazolidinone ring. The pharmaceutically active enantiomer is of the formula (IA):



(IA)

The present invention includes the pure enantiomer depicted above or mixtures of the 5R and 5S enantiomers, for example a racemic mixture. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted above is the 5R enantiomer.

Furthermore, some compounds of the formula (I) may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereo-isomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by

biotransformation or by chromatographic separation) and how to determine antibacterial activity as described hereinafter.

The invention relates to all tautomeric forms of the compounds of the formula (I) that possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) may exhibit polymorphism, and that the invention encompasses all such forms which possess antibacterial activity.

As stated before, we have discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics. Physical and/or pharmacokinetic properties, for example increased stability to mammalian peptidase metabolism and a favourable toxicological profile are important features. The following compounds possess particularly favourable physical and/or pharmacokinetic properties and are preferred.

Particularly preferred compounds of the invention comprise a compound of formula (I) or of formula (IP), or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein the substituents Q, X, HET, T and other substituents mentioned above have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

Preferably Q is selected from Q1, Q2, Q4, Q6 and Q9; especially Q1, Q2 and Q9; more particularly Q1 and Q2; and most preferably Q is Q1.

Preferably T is selected from (TAf), (TDb) or (TC); especially groups (TCb) and (TCc); more particularly (TC2), (TC3) and (TC4); and most preferably (TC5), (TC7) or (TC9), and most particularly (TC5). Especially preferred is each of these values of T when present in Q1 and Q2, particularly in Q1.

Preferable values for other substituents (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter) are :-

(a) Preferably X is -O-;

(a1) In another aspect X is -S-;

(b) Preferably HET is pyrazole, imidazole, oxazole, isoxazole, 1,2,4- oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, isothiazole or 1,2,5-thiadiazole. Yet more preferably HET is pyrazol-3-yl, imidazol-2-yl, oxazol-2-yl, isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl;

(b1) Especially preferred is HET as isoxazole (optionally substituted as disclosed hereinbefore), particularly isoxazol-3-yl;

(b2) In another embodiment HET is as defined hereinbefore or hereinafter, but excluding thiazole and thiadiazole; and in another embodiment HET is as defined hereinbefore or hereinafter, but excluding isothiazole and thiadiazole;

(b3) Preferably HET is unsubstituted;

(c) Preferably Rp is hydrogen;

(d) Preferably Rp1 and Rp2 are independently selected from hydrogen, (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl;

(e) Most preferably Rp1 and Rp2 are hydrogen;

(f) Preferably one of R^2 and R^3 is hydrogen and the other fluoro;

(g) In another aspect both R^2 and R^3 are fluoro;

(h) Preferably >A-B- is of the formula >C=CH- (i.e. Rr is preferably hydrogen) or >N-CH_2-;

(i) Preferably D is -O- or >NRcp;

(j) Preferably Rcp is AR, R^{13p}CO-, $R^{13p}SO_2$-, R^{13p}CS-;

(k) More preferably Rcp is AR (most preferably benzyl, pyrimidyl, pyridinyl, pyridazinyl or pyrazinyl) or R^{13p}CO- (especially R^{13p}CO-);

(l) Preferably AR is 5- or 6-membered heteroaryl; more preferably AR is 6-membered heteroaryl, such as pyridinyl;

(m) Preferred substituents for phenyl and carbon atoms in heteroaryl (mono- and bicyclic) ring systems in AR, R^{14p} and Ri include halo, (1-4C)alkyl, hydroxy, nitro, amino, cyano, (1-4C)alkyl$S(O)_p$- and (1-4C)alkoxy;

(n) Preferably the optionally substituted ring systems in AR, R^{14p} and Ri are unsubstituted;

(n1) In another embodiment in the definition of R^{13p} in (PC) of embodiment (IP), 1,3-

dioxolan-4-yl and 1,4-dioxan-2-yl are excluded.

(o) Preferably R^{13p} is (1-4C)alkoxycarbonyl, hydroxy(1-4C)alkyl, (1-4C)alkyl (optionally substituted by one or two hydroxy groups, or by an (1-4C)alkanoyl group), (1-4C)alkylamino, dimethylamino(1-4C)alkyl, (1-4C)alkoxymethyl, (1-4C)alkanoylmethyl, (1-4C)alkanoyloxy(1-4C)alkyl, (1-5C)alkoxy or 2-cyanoethyl;

(p) More preferably R^{13p} is 1,2-dihydroxyethyl, 1,3-dihydroxyprop-2-yl, 1,2,3-trihydroxyprop-1-yl, methoxycarbonyl, hydroxymethyl, methyl, methylamino, dimethylaminomethyl, methoxymethyl, acetoxymethyl, methoxy, methylthio, naphthyl, tert-butoxy or 2-cyanoethyl;

(p1) Yet more preferably R^{13p} is 1,2-dihydroxyethyl, 1,3-dihydroxyprop-2-yl or 1,2,3-trihydroxyprop-1-yl;

(q) Preferred optional substituents for (1-10C)alkyl in R^{14p} are hydroxy, cyano, amino, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-4C)alkyl$S(O)_p$- (wherein p is 1 or 2), carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkoxy, piperazino or morpholino;

(r) Preferred optional substituents for (1-6C)alkyl in R^{15p} are hydroxy, (1-4C)alkoxy, cyano, amino, (1-4C)alkylamino, di((1-2C)alkyl)amino, (1-4C)alkyl$S(O)_p$- (wherein p is 1 or 2);

(s) Preferably 5- or 6-membered heteroaryl in R^{14p} is pyridinyl or imidazol-1-yl;

(t) Preferably R^{15p} is (1-6C)alkyl; most preferably R^{15p} is tert-butyl or methyl;

(u) Preferably R^{17p} is cyano or fluoro;

(v) Preferably R^{16p} is hydrogen;

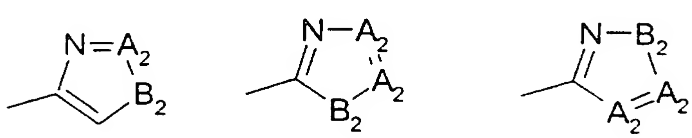
(w) Preferably CY is naphthoxy, especially naphth-1-oxy or naphth-2-oxy.

Where preferable values are given for substituents in a compound of formula (IP), the corresponding substituents in a compound of formula (I) have the same preferable values (thus, for example, R^{13} and Rc in formula (I) correspond with Rcp and R^{13p} in formula (IP), and similarly for groups D and G). For compounds of formula (I) preferred values for Rc are those in group (Rc2). The preferred values for R^{13p} listed above for compounds of formula (IP) are also preferred values for R^{13} in compounds of formula (I). In the definition of (Rc2c) the AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups are preferably excluded.

In another aspect, HET is a C-linked 5-membered heteroaryl ring containing 2 or 3

heteratoms independently selected from N, O and S (with the proviso that there are no O-O, O-S, S-S or N-S bonds), which ring is optionally substituted on any available C atom (provided that when a N atom is adjacent to the X-link, there is no substitution on any C atom that is adjacent to this N atom) by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available N atom (provided that the ring is not thereby quaternised), by (1-4C)alkyl.

In another aspect, HET is selected from the formulae (HET1) to (HET3) below :-



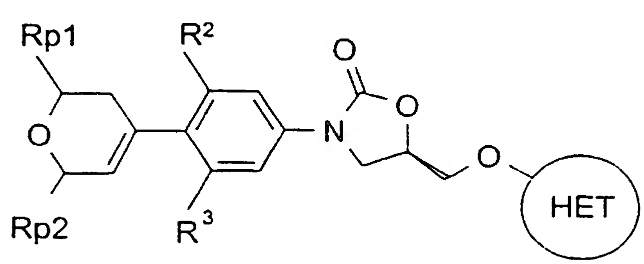
(HET1) (HET2) (HET3)

wherein A_2 is carbon or nitrogen and B_2 is O, S or N (with a maximum of 3 hetero atoms per ring), with carbon or nitrogen ring atoms being optionally substituted as described for HET hereinbefore (preferably with no substitution on any carbon atom that is adjacent to the specified N atom).

In another embodiment HET is as defined herein and also optionally substituted on an available suitable C atom by (1-4C)alkoxycarbonyl.

The above HET definitions are especially preferred in embodiment (IP), and with preferable value (n1) of R^{13p}.

Especially preferred compounds of the present invention are of the formula (IB):



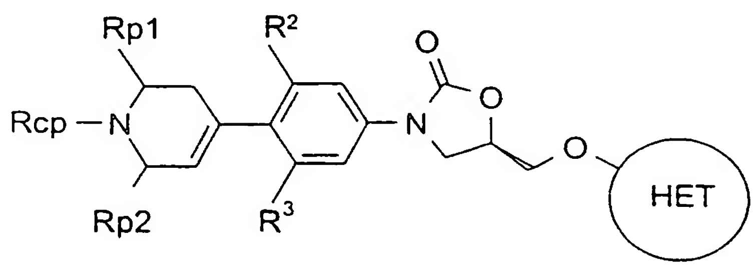
(IB)

wherein HET is isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl; R^2 and R^3 are independently hydrogen or fluoro; and Rp1 and Rp2 are independently hydrogen, hydroxy, bromo, (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl; or pharmaceutically-acceptable salts thereof.

Further especially preferred compounds of the invention are of the formula (IB) wherein HET is isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl; R^2 and R^3 are independently hydrogen or fluoro; and Rp1 and Rp2 are independently hydrogen, AR-oxymethyl or AR-thiomethyl (wherein AR is phenyl, phenyl-(1-4C)alkyl, naphthyl, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole or thiophene); or pharmaceutically-acceptable salts thereof.

Of the above especially preferred compounds of the invention of the formula (IB), particularly preferred compounds are those wherein Rp1 and Rp2 are hydrogen are particularly preferred.

Further, especially preferred compounds of the invention are of the formula (IC):



(IC)

wherein HET is isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl; R^2 and R^3 are independently hydrogen or fluoro; Rp1 and Rp2 are independently hydrogen, AR-oxymethyl or AR-thiomethyl (wherein AR is phenyl, phenyl-(1-4C)alkyl, naphthyl, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole or thiophene), (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl and Rcp is cyano, pyrimidin-2-yl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl or Rcp is of the formula $R^{13p}CO$-, $R^{13p}SO_2$- or $R^{13p}CS$- (wherein R^{13p} is hydrogen, (1-5C)alkyl [optionally substituted by one or more groups each independently selected from hydroxy and amino, or optionally monosubstituted by (1-4C)alkoxy, (1-4C)alkylS(O)$_q$-, (1-4C)alkylamino, (1-4C)alkanoyl, naphthoxy, (2-

6C)alkanoylamino or (1-4C)alkylS(O)$_p$NH- wherein p is 1 or 2 and q is 0, 1 or 2], imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, pyridoimidazole, pyrimidoimidazole, quinoxaline, quinazoline, phthalazine, cinnoline or naphthyridine, or R^{13p} is of the formula R^{14p}C(O)O(1-6C)alkyl wherein R^{14p} is (1-6C)alkyl), or Rcp is of the formula RfC(=O)C(=O)- wherein Rf is (1-6C)alkoxy; or pharmaceutically-acceptable salts thereof.

Of the above especially preferred compounds of the invention of the formula (IC), those wherein HET is isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl; R^2 and R^3 are independently hydrogen or fluoro; Rp1 and Rp2 are independently hydrogen, AR-oxymethyl or AR-thiomethyl (wherein AR is phenyl, phenyl-(1-4C)alkyl, naphthyl, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole or thiophene), (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl and Rcp is cyano, pyrimidin-2-yl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl or Rcp is of the formula R^{13p}CO-, $R^{13p}SO_2$- or R^{13p}CS- (wherein R^{13p} is hydrogen, (1-5C)alkyl [optionally substituted by one or more groups each independently selected from hydroxy and amino, or optionally monosubstituted by (1-4C)alkoxy, (1-4C)alkylS(O)$_q$, (1-4C)alkylamino, (1-4C)alkanoyl, (2-6C)alkanoylamino or (1-4C)alkylS(O)$_p$NH- wherein p is 1 or 2 and q is 0, 1 or 2], pyridine, or R^{13p} is of the formula R^{14p}C(O)O(1-6C)alkyl wherein R^{14p} is (1-6C)alkyl), or Rcp is of the formula RfC(=O)C(=O)- wherein Rf is (1-6C)alkoxy; or pharmaceutically-acceptable salts thereof are further preferred.

Of the above especially preferred compounds of the invention of the formula (IC), particularly preferred compounds are those wherein HET is isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl; R^2 and R^3 are independently hydrogen or fluoro; Rp1 and Rp2 are hydrogen, and Rcp is pyridin-2-yl (optionally substituted with cyano) or Rcp is of the formula R^{13p}CO- (wherein R^{13p} is hydrogen, 1,3-dioxolan-4-yl (optionally disubstituted with (1-4C)alkyl) or (1-5C)alkyl [optionally substituted by one or more hydroxy groups] or R^{13p} is of the formula R^{14p}C(O)O(1-6C)alkyl wherein R^{14p} is (1-6C)alkyl)); or pharmaceutically-acceptable salts thereof.

Of the above especially preferred compounds of the invention of the formula (IC), particularly preferred compounds are those wherein Rcp is of the formula R^{13p}CO- (wherein

R^{13p} is hydrogen, 1,3-dioxolan-4-yl (optionally disubstituted with (1-4C)alkyl) or (1-5C)alkyl [substituted by two hydroxy groups]; or pharmaceutically-acceptable salts thereof.

In another aspect of the invention all of the compounds of formula (IB) or (IC) described above are further preferred when HET is isoxazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl.

In yet another aspect the invention relates to all of the compounds of formula (IB) or (IC) described above wherein HET is isoxazol-3-yl or 1,2,4-oxadiazol-3yl.

In yet another aspect the invention relates to all of the compounds of formula (IB) or (IC) described above wherein HET is isoxazol-3-yl.

In another aspect of the invention there are provided preferred compounds of the formula (IP) wherein -X-HET is isoxazol-3-yloxy, 1,2,4-oxadiazol-3-yloxy, isothiazol-3-yloxy, 1,2,5-thiadiazol-3-yloxy; >A-B- is >N-CH_2- and D is NRcp wherein Rcp is a 6-membered heteroaryl ring containing 1, 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl, halo, trifluoromethyl, (1-4C)alkyl $S(O)_q$- (wherein q is 0, 1 or 2), (1-4C)alkyl$S(O)_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, (1-4C)alkoxy, cyano or nitro; or pharmaceutically-acceptable salts thereof.

In all of the above aspects and preferred compounds of formula (IB) or (IC), in-vivo hydrolysable esters are preferred, especially phosphoryl esters (as defined by formula (PD3) with npd as 1).

In all of the above definitions the preferred compounds are as shown in formula (IA), i.e. the pharmaceutically active (5(R)) enantiomer.

Particular compounds of the present invention include the following (and the individual isomers where a mixture of isomers is possible) :-

5(R)-Isoxazol-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(5-Methylisoxazol-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(R,S)-ylcarbonyl)-5,6-

tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)-oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-formyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-acetoxyacetyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-hydroxyacetyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one:

5(R)-Isothiazol-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(1,2,5-Thiadiazol-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one; or pharmaceutically-acceptable salts thereof.

Of the above compounds, especially preferred is (and the individual isomers thereof) :-
5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)-oxazolidin-2-one; or pharmaceutically-acceptable salts or in-vivo hydrolysable esters thereof.

Also preferred are the 3-fluorophenyl analogues of the particular 3,5-difluoro compounds mentioned above.

Other preferred Examples if not already specifically mentioned are Example Nos. 1, 2, 7, 14, 48, 148, 151 and 23.

Also preferred is the compound (and the individual isomers thereof) :-
5(R)-Isothiazol-3-yloxymethyl-3-(4-(1-(2(R,S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)-oxazolidin-2-one; or pharmaceutically-acceptable salts or in-vivo hydrolysable esters thereof.

Most particularly preferred Examples are Example Nos. 12, 18, 19, 20, 21 and 22 or pharmaceutically-acceptable salts. In-vivo hydrolysable esters of Examples 12 and 18 are preferred, especially phosphoryl esters.

Thus, preferred are the compounds, or pharmaceutically-acceptable salts thereof :-

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-diphosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-diphosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one.

Also preferred are the compounds, or pharmaceutically-acceptable salts thereof :-

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one.

Also preferred are the compounds, or pharmaceutically-acceptable salts thereof :-

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-hydroxy-2(S)-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-hydroxy-2(S)-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one.

Suitable pharmaceutically-acceptable salts of the last two named compounds and of Example Nos. 19, 20, 21 and 22 are the mono- and di- salts of the mono-phosphoryl ester compounds and the mono-, di-, tri- and tetra- salts of the di-phosphoryl ester compounds (Examples 19 and 21). Particularly preferred salts are the sodium salts.

Process section :

In a further aspect the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Examples of the use of resins as a protecting group are illustrated in Examples 135 & 136 herein.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the following Patent and Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference :

WO99/02525; WO98/54161; WO97/37980; WO97/30981 (& US5,736,545); WO97/21708 (& US5,719,154); WO97/10223; WO97/09328; WO96/35691; WO96/23788; WO96/15130; WO96/13502; WO95/25106 (& US5,668,286); WO95/14684 (& US5,652,238); WO95/07271 (& US5,688,792); WO94/13649; WO94/01110; WO93/23384 (& US5,547,950 & US 5,700,799); WO93/09103 (& US5,565,571, US5,654,428, US5,654,435, US5,756,732 & US5,801,246); US5,231,188; US5,247,090; US5,523,403; WO97/27188; WO97/30995; WO97/31917; WO98/01447; WO98/01446; WO99/10342; WO99/10343; WO99/11642; European Patent Application Nos. 0,359,418 and 0,609,905; 0,693,491 A1 (& US5,698,574); 0,694,543 A1 (& AU 24985/95); 0,694,544 A1 (& CA 2,154,024); 0,697,412 A1 (& US5,529,998); 0,738,726 A1 (& AU 50735/96); 0,785,201 A1 (& AU 10123/97); German Patent Application Nos. DE 195 14 313 A1 (& US5,529,998); DE 196 01 264 A1 (& AU 10098/97); DE 196 01 265 A1 (& AU 10097/97); DE 196 04 223 A1 (& AU 12516/97); DE 196 49 095 A1 (& AU 12517/97).

The following Patent and Application Publications may also provide useful information and the contents of the relevant process sections are hereby incorporated herein by reference :

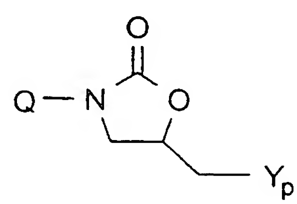
FR 2458547; FR 2500450(& GB 2094299, GB 2141716 & US 4,476,136); DE 2923295 (& GB 2028306, GB 2054575, US4,287,351, US4,348,393, US4,413,001, US4,435,415 & US4,526,786), DE 3017499 (& GB 2053196, US4,346,102 & US4,372,967); US4,705,799; European Patent Application Nos. 0,312,000; 0,127,902; 0,184,170; 0,352,781; 0,316,594;

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references to obtain necessary starting materials.

Thus, the present invention also provides that the compounds of the formulae (I) and pharmaceutically-acceptable salts and *in vivo* hydrolysable esters thereof, can be prepared by a process **(a)** to **(i)** as follows (wherein the variables are as defined above unless otherwise stated) :

(a) by modifying a substituent in or introducing a substituent into another compound of formula (I);

(b) by reaction of a compound of formula (II)



(II)

wherein Yp is hydroxy with a compound of the formula (b1) HET-OH or (b2) HET-Lg, wherein Lg is a suitable leaving group;

(c) by reaction of a compound of formula (II) wherein Yp is a leaving group, for example halogen, mesylate or tosylate, with a metal alkoxide compound of the formula HET-OM where M is an alkali metal, or another metal, such as silver, known to promote O-alkylation;

(d) by reaction of a compound of the formula Q-Zp wherein Zp is an isocyanate or amine group with an epoxide of the formula $CH_2(O)CH$-CH_2O-HET;

(e) when X is -S- by a process analogous to process (c) wherein (e1) a metal thioxide compound of the formula HET-SM where M is an alkali metal, or another metal, such as

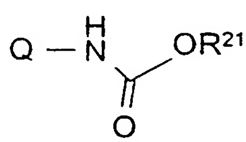
silver, known to promote S-alkylation; or (e2) alternatively by a process analogous to process (c) using HET-SH and a compound of formula (II) in which Yp is a suitable leaving group;

(f) when X is -SO- or -SO_2- by oxidation of a compound wherein X is -S-;

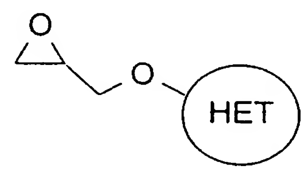
(g) by conversion to a non-quaternary compound of a compound of formula (I) in which the ring HET bears a quaternary nitrogen;

(h) when HET is an isoxazole ring by reaction of a compound of the formula (II) in which Yp is -O-CH=N-OH with an acetylene;

(i) by reaction of a urethane compound of formula (III) with a compound of formula (IV)



(III)



(IV)

wherein R^{21} is (1-6C)alkyl or benzyl; and thereafter if necessary :

(i) removing any protecting groups; (ii) forming a pharmaceutically-acceptable salt; (iii) forming an *in vivo* hydrolysable ester.

General guidance on reaction conditions and reagents may be obtained in Advanced Organic Chemistry, 4th Edition, Jerry March (publisher : J.Wiley & Sons), 1992. Necessary starting materials may be obtained by standard procedures of organic chemistry, such as described in this process section, in the Examples section or by analogous procedures within the ordinary skill of an organic chemist. Certain references are also provided (see above) which describe the preparation of certain suitable starting materials, for particular example see International Patent Application Publication No. WO 97/37980, the contents of which are incorporated here by reference. Processes analogous to those described in the references may also be used by the ordinary organic chemist to obtain necessary starting materials.

(a) Methods for converting substituents into other substituents are known in the art. For example an alkylthio group may be oxidised to an alkylsulfinyl or alkylsulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, a hydroxy group thiomethylated to an arylthiomethyl or a heteroarylthiomethyl group (see, for example, Tet.Lett., 585. 1972), a carbonyl group

converted to a thiocarbonyl group (eg. using Lawsson's reagent) or a bromo group converted to an alkylthio group. It is also possible to convert one Rc group into another Rc group as a final step in the preparation of a compound of the formula (I).

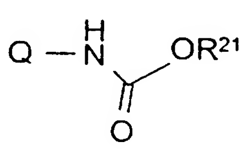
One compound of formula (I) may be converted into another compound of formula (I) by reacting a compound of formula (I) in which T is halo with a suitable compound to form another value of T. Thus, for example, T as halo may be displaced by suitable vinyl, aromatic, tropolone and nitrogen-linked systems as T by reaction using known Pd(0) coupling techniques.

Further examples of converting substituents into other substituents are contained in the accompanying non-limiting Examples.

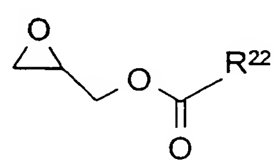
(b1) When HET-OH is used reaction (b1) is performed under Mitsunobu conditions, for example, in the presence of tri-n-butylphosphine and diethyl azodicarboxylate (DEAD) in an organic solvent such as THF, and in the temperature range 0°C - 60°C, but preferably at ambient temperature. Details of Mitsunobu reactions are contained in Tet. Letts., 31, 699, (1990); The Mitsunobu Reaction, D.L.Hughes, Organic Reactions, 1992, Vol.42, 335-656 and Progress in the Mitsunobu Reaction, D.L.Hughes, Organic Preparations and Procedures International, 1996, Vol.28, 127-164.

(b2) When HET-Lg is used reaction (b2) is performed using a suitably reactive HET and under basic conditions (using a base such as 1,8-diazabicyclo[5,4,0]undec-7-ene) which are sufficiently mild not to destroy the oxazolidinone ring structure. The skilled organic chemist will appreciate which suitable leaving group Lg (such as chloro or bromo) and reaction conditions to use.

Compounds of the formula (II) wherein Yp is hydroxy may be obtained by reacting a compound of the formula (III) with a compound of formula (V):



(III)



(V)

wherein R^{21} is (1-6C)alkyl or benzyl and R^{22} is (1-4C)alkyl or $-S(O)_q$(1-4C)alkyl where q is 0, 1 or 2. Preferably R^{22} is (1-4C)alkyl.

Compounds of the formula (II), (III) and (V) may be prepared by the skilled chemist, for example as described in International Patent Application Publication Nos. WO95/07271, WO97/27188, WO 97/30995, WO 98/01446 and WO 98/01446, the contents of which are hereby incorporated by reference, and by analogous processes.

If not commercially available, compounds of the formula HET-OH and HET-Lg may be prepared by procedures which are selected from standard chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the procedures described in the Examples. For example, standard chemical techniques are as described in Houben Weyl, Methoden der Organische Chemie, E8a, Pt.I (1993), 45-225, B.J.Wakefield (for isoxazoles) and E8c, Pt.I (1994), 409-525, U.Kraatz (for 1,2,4-oxadiazoles). Also, for example, 3-hydroxyisoxazole may be prepared by cyclisation of CH≡C-CO-NHOH (prepared from CH≡C-CO-O-(1-4C)alkyl) as described in Chem.Pharm.Bull.Japan, 14, 92, (1966).

(c) & (e) Reactions (c) and (e) are performed conveniently at a temperature in the range 25-60°C in a solvent such as NMP or DMF.

A compound of the formula (II) wherein Yp is fluoro may be prepared by reacting a compound of the formula (II) wherein Yp is hydroxy (hydroxy compound) with a fluorinating agent such as diethylaminosulfur trifluoride in an organic solvent such as dichloromethane in the temperature range of 0°C to ambient temperature.

When Yp is chloro. the compound of the formula (II) may be formed by reacting the hydroxy compound with a chlorinating agent. For example, by reacting the hydroxy compound with thionyl chloride, in a temperature range of ambient temperature to reflux, optionally in a chlorinated solvent such as dichloromethane or by reacting the hydroxy compound with carbon tetrachloride/triphenyl phosphine in dichloromethane, in a temperature range of 0°C to ambient temperature. A compound of the formula (II) wherein Yp is chloro or iodo may also be prepared from a compound of the formula (II) wherein Yp is mesylate or tosylate, by reacting the latter compound with lithium chloride or lithium iodide and crown ether, in a suitable organic solvent such as THF, in a temperature range of ambient temperature to reflux

When Yp is (1-4C)alkanesulfonyloxy or tosylate the compound (II) may be prepared by reacting the hydroxy compound with (1-4C)alkanesulfonyl chloride or tosyl chloride in the

presence of a mild base such as triethylamine or pyridine.

Compounds of the formula HET-OM and HET-SM may be prepared by the skilled chemist from the corresponding HET-OH or HET-SH compound, using a suitable base, such as sodium hydride, silver carbonate, sodium carbonate or an alkoxide.

When X is -S- and a process is used that is analogous to process (c) but using HET-SH and a compound of formula (II) in which Yp is a suitable leaving group, a suitable leaving group is, for example, mesylate and a suitable base for the reaction is a base such as 1,8-diazabicyclo[5,4,0]undec-7-ene (see for example, Example 153).

(d) Reaction (d) is performed under conditions analogous to those described in the following references which disclose how suitable and analogous starting materials may be obtained.

Compounds of the formula Q-Zp wherein Zp is an isocyanate may be prepared by the skilled chemist, for example by analogous processes to those described in Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165. Compounds of the formula Q-Zp wherein Zp is a urethane (see process (i)) may be prepared by the skilled chemist, for example by analogous processes to those described in International Patent Application Publication Nos. WO 97/30995 and WO 97/37980.

A similar reaction to reaction (d) may be performed in which Q-Zp wherein Zp is a amine group is reacted with the epoxide (optionally in the presence of an organic base), and the product is reacted with, for example, phosgene to form the oxazolidinone ring. Such reactions and the preparation of starting materials in within the skill of the ordinary chemist with reference to the above-cited documents disclosing analogous reactions and preparations.

Epoxides of the formula $CH_2(O)CH-CH_2O$-HET may be prepared from the corresponding $CH_2=CH-CH_2$-O-HET compound. Certain such epoxide and alkene intermediates are novel and are provided as a further feature of the invention. For example, when HET is isoxazol-3-yl, 3-(2,3-oxiranepropyloxy)isoxazole may be prepared from 3-allyloxyisoxazole. Asymmetric epoxidation may be used to give the desired optical isomer.

(f) When X is -SO- or $-SO_2-$ the oxidation of a compound wherein X is -S- may be achieved by oxidising with standard reagents known in the art for the oxidation of a thio group to a sulfinyl or sulfonyl group. For example, a thio group may be oxidised to a sulfinyl group with a peracid such as m-chloroperoxybenzoic acid and oxidising agents such as

potassium permanganate can be used to convert a thio group to a sulfonyl group.

(g) The conversion to a non-quaternary compound of a compound of formula (I) in which the ring HET bears a quaternary nitrogen may be achieved under thermal conditions suitable to achieve elimination of the quaternary group (for example, a methyl group will be eliminated as a methyl halide).

A compound of formula (I) in which the ring HET bears a quaternary nitrogen may be prepared in a similar manner to the conditions described for reaction (c), although a suitably quaternised HET compound, substituted in the alpha position next to nitrogen by a leaving group (such as halogen), and a compound of the formula (II) in which Yp is -OH or -SH, is used. Such starting materials are readily prepared by the ordinary organic chemist.

A compound of formula (I) in which the ring HET bears a quaternary nitrogen may also be prepared in a similar manner to the conditions described in Chem.Pharm.Bull.Japan, 27, 2415-2423, (1979), by reaction of an N-alkylated HET-OH or HET-SH compound in the keto-form (with the keto (oxo or thioxo) group in the alpha position next to nitrogen) with a compound of formula (II) in which Yp is a leaving group such as mesylate.

(h) When the HET ring is isoxazole it may be built up as a final step from a compound of the formula (II) in which Yp is -O-CH=N-OH by reaction under standard conditions with an acetylene (see for example, Acta Chem. Scand 47, 1004, 1993).

(i) A compound of formula (III) is reacted with a compound of formula (IV) using similar conditions to those for reaction of a compound of the formula (III) with a compound of formula (V) described above. If not commercially available, the preparation of suitable starting materials of formulae (III) and (IV) is as described above, or by using analogous processes.

The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an *in vivo* hydrolysable ester are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps, for example the preparation of in-vivo hydrolysable ester prodrugs has been provided in the section above on such esters, and in certain of the following non-limiting Examples.

When an optically active form of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by

resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the formula (I), an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, aerosols (or sprays), drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 1mg and 1g of a compound of this invention, preferably between 100mg and 1g of a compound. Especially preferred is a tablet or capsule which contains between 50mg and 800mg of a compound of this invention, particularly in the range 100mg to 500mg.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example an injection which contains between 0.1% w/v and 50% w/v (between 1mg/ml and 500mg/ml) of a compound of this invention.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 0.5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention, the composition being administered 1 to 4 times per day. In another embodiment a daily dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention is administered. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time.

Alternatively each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

A pharmaceutical composition to be dosed intravenously may contain advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Antibacterial Activity :

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity against enterococci, pneumococci and methicillin resistant strains of S.aureus and coagulase negative staphylococci. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The (antibacterial) properties of the compounds of the invention may also be demonstrated and assessed in-vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal using standard techniques.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot. Typically, compounds are active in the range 0.01 to 256 μg/ml.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms.

Organism		MIC (µg/ml)			
		Example 4	Example 12	Example 18	Example 151
Staphylococcus aureus:					
	Oxford	0.25	0.25	0.25	0.13
	Novb. Res	0.50	0.5	0.25	0.25
	MRQR	0.50	0.5	0.5	0.25
Coagulase Negative Staphylococci					
	MS	0.13	0.13	0.13	0.13
	MR	0.50	0.5	0.5	0.25
Streptococcus pyogenes					
	C203	0.50	0.5	0.25	0.25
Enterococcus faecalis		1.00	1.00	0.5	0.25
Bacillus subtilis		0.25	0.25	0.25	0.13

Novb. Res = Novobiocin resistant

MRQR = methicillin resistant quinolone resistant

MR = methicillin resistant

MS = methicillin sensitive

Certain Reference Examples described hereinafter (for example, Reference Examples 9, 10, 11, 30, 38 & 39) may also possess useful activity.

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

i) evaporations were carried out by rotary evaporation <u>in vacuo</u> and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the formula (I) were generally confirmed by NMR

and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected];

(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis; and

(vii) in which the following abbreviations may be used :-

® is a Trademark; DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; ESP is electrospray; THF is tetrahydrofuran; TFA is trifluoroacetic acid; NMP is N-methylpyrrolidone; HOBT is 1-hydroxy-benzotriazole; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; phosphiryl is $(HO)_2$-P-O-; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (hydrochloride); PTSA is para-toluenesulfonic acid.

Example 1: 5(R)-Isoxazol-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

Diisopropylazodicarboxylate (248mg, 1.22 mmol) was added dropwise, at ambient temperature, to a stirred solution of 5(R)-hydroxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one (International Patent Application Publication WO 97/09328) (300mg, 1.02mmol), 3-hydroxyisoxazole (104mg, 1.22mmol) and triphenylphosphine (340mg, 1.30mmol) in THF (8.0ml). The resulting solution was stirred at ambient temperature for 30 minutes before evaporating the solvent to give an oil which was purified by flash chromatography (Merck 9385 silica, EtOAc / iso-hexane (7:3) eluant) to give the title product (219mg, 59%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.45–2.55 (m, 2H), 3.88-4.00 (m, 3H), 4.17 (t, 1H), 4.33 (m, 2H), 4.50 (dd, 1H), 4.58 (dd, 1H), 5.04 (m, 1H), 6.01 (d, 1H), 6.06 (m, 1H), 7.22-7.32 (m, 2H), 7.42 (d, 1H), 8.15 (d, 1H). MS: ESP$^+$ $(M+H)^+$= 361.

Example 2: 5(R)-(5-Methylisoxazol-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

5(R)-hydroxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one (300mg, 1.02mmol), 3-hydroxy-5-methylisoxazole (120mg, 1.21mmol), triphenylphosphine (270mg, 1.03mmol) and diisopropylazodicarboxylate (204mg, 1.01mmol) were reacted in THF (8.0ml) using the general method of Example 1. The resultant product was purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (7:3) eluant) to give the title product (176mg, 46%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.34 (s, 3H), 2.45-2.55 (m, 2H), 3.86-4.00 (m, 3H), 4.14 (t, 1H), 4.32 (m, 2H), 4.46 (dd, 1H), 4.54 (dd, 1H), 5.02 (m, 1H), 5.65 (s, 1H), 6.05 (m, 1H), 7.20-7.32 (m, 2H), 7.42 (d, 1H). MS: ESP$^+$ $(M+H)^+$ = 375.

Reference Example 1: 3,5-Difluoro-4-(1-benzyl-4-hydroxyhexahydropyrid-4-yl)aniline

nBuLi (1.32M in hexanes, 350ml, 0.462 mol) was added dropwise over 20 minutes to a solution of N,N-(1,2-bis(dimethylsilyl)ethane)-3,5-difluoroaniline, (108.4g, 0.40mol, J. Org. Chem., 60, 5255-5261 (1995)) in 800ml dry THF at -70°C under argon. After stirring for a further 4 hours at -70°C, N-benzyl-4-piperidone (87.8g, 0.46mol) in 270ml dry THF was added dropwise over 40 minutes at the same temperature and the reaction allowed to stir to

ambient temperature overnight. Solvent was removed in vacuo and the resultant product treated with ice and conc.HCl and extracted with ether. The aqueous acidic phase was then treated with 40% NaOH with cooling, extracted with ether (and worked up by washing with water, with brine and drying with an anhydrous drying agent such as magnesium sulfate or sodium sulfate before evaporation - this work up procedure is referred to as work up in the usual manner hereinafter) to give 144.7g of a sludge. Analysis by TLC using 10% MeOH/dichloromethane on silica indicated that the desired alcohol was present as approximately 90% of the product, and the crude product was used without further purification. MS: ESP+ (M+H) = 319.

Reference Example 2: 3,5-Difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline

The crude product from Reference Example 1 (144.7g) was suspended in 400ml conc.HCl and heated at reflux with stirring for 18 hours. TLC showed all starting material had reacted, and after cooling in ice the reaction mixture was taken to pH 11 with conc. NH_3 (aq) and extracted three times with dichloromethane. Usual work-up gave 119.5g of a viscous oil. TLC indicated a purity of ca. 80% and the crude product was used without further purification. MS: ESP+ (M+H) = 301.

Reference Example 3: N-Benzyloxycarbonyl-3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline

The crude aniline from Reference Example 2 (3.2g, 10.7mmol) in 10ml of acetone was added in one portion to a stirred solution of sodium dihydrogen phosphate (3.0g) in 30ml water. The resulting mixture was cooled to 5-10^{o}C and a solution of benzylchloroformate (2.18g, 1.8ml, 12.8mmol) in 10ml of acetone was added dropwise. The mixture was stirred for a further hour at ice-bath temperature and then at ambient temperature for 2 hours. The mixture was diluted with 80ml water, basified with conc.NH_3(aq) and extracted with EtOAc. Usual work-up gave a viscous oil which was purified by flash chromatography (Merck 9385 silica, EtOAc/isohexane (3:7 eluant) and triturated with isohexane to give a solid (1.53g 33%). MS: ESP+ (M+H) = 434.

Reference Example 4: 5(R)-Hydroxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The benzylurethane from Reference Example 3 (5.54g, 12.76mmol) in 50ml dry THF was cooled to -70^{0}C under nitrogen and 8.80ml of 1.6M nBuLi in hexanes (14.08mmol) added dropwise at the same temperature. After 20 minutes at the same temperature a solution of (R)-glycidyl butyrate (2.00g, 13.88mmol in 5ml THF) was added dropwise and the mixture stirred for 30 minutes at -70^{0}C, and then stirred to ambient temperature overnight. After quenching with 100ml 10% ammonium chloride, the mixture was extracted with EtOAc and usual work-up to give an oily solid, which was purified by flash chromatography (Merck C60 silica, 5% MeOH/dichloromethane eluant) to give a crystalline solid (4.40g, 86%). MS: ESP+ (M+H) = 401.

^{1}H-NMR (250MHz, DMSO-d6): δ = 2.32 (m, 2H), 2.63 (t, 2H), 3.05 (m, 2H), 3.50-3.72 (m,4H), 3.82 (dd,1H), 4.06 (t,1H), 4.73 (m,1H), 5.18 (t,1H), 5.78 (m,1H).

Reference Example 5: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 4 (2.6g, 6.5mmol), 3-hydroxyisoxazole (0.60g, 7.06mmol), triphenylphosphine (1.96g, 7.48mmol) and diisopropylazodicarboxylate (1.44g, 7.13mmol) in THF (40ml) were reacted using the general method of Example 1. The resultant product was purified by flash chromatograpy (Merck 9385 silica, EtOAc / isohexane (3:2) eluant initially, then repeated using methyl tert-butylether eluant) to give the title product (2.6g, 86%) as a gum. MS: ESP$^+$ (M+H)$^+$= 468.

Reference Example 6: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 5 (2.6g, 5.57mmol) in dichloromethane (40ml) was cooled, under an atmosphere of nitrogen, in an ice-water bath then 1-chloroethyl chloroformate (0.80g, 5.59mmol) added dropwise via syringe. The resulting solution was stirred at ice temperature for 1 hour before isolating the intermediate product (carbamate) by flash chromatograhy (Merck 9385 silica, EtOAc / isohexane (1:1) eluant). The resulting gum was taken up in MeOH (40ml) and refluxed for 1 hour. Evaporation of the solvent after this time gave the title product (1.46g, 64%) as a crystalline solid.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.54 (m, 2H), 3.27 (m, 2H), 3.72 (m, 2H), 3.92 (dd, 1H), 4.20 (t, 1H), 4.38-4.52 (m, 2H), 5.10 (m, 1H), 5.88 (m, 1H), 6.38 (d, 1H), 7.37 (m, 2H), 8.68 (d, 1H), 9.39 (s(broad), 2H). MS: ESP$^+$ (M+H)$^+$=378.

Example 3: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(R,S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (160mg, 0.84mmol) was added portionwise at ambient temperature to a stirred mixture of Reference Example 6 (300mg, 0.72mmol), (R/S)-2,3-O-isopropylideneglyceric acid (122mg, 0.84mmol) and triethylamine (73mg, 0.72mmol) in dichloromethane (6ml). The resulting mixture was stirred for 3 hours then left to stand overnight before washing with water. The dichloromethane solution was purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (3:1) eluant) to give the title product (143mg, 39%) as a crystalline solid. MS: ESP$^+$ (M+H)$^+$=506. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.41 (s, 6H), 2.35-2.65 (m, 2H), 3.65-3.80 (m, 1H), 3.92-4.00 (m, 2H), 4.10-4.22 (m, 3H), 4.22-4.45 (m, 1H), 4.45-4.62 (m, 3H), 4.75 (t, 1H), 5.05 (m, 1H), 5.80-5.91 (m, 1H), 6.01 (d, 1H), 7.18 (m, 2H), 8.16 (d, 1H).

Example 4: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)-oxazolidin-2-one

Example 3 (194mg, 0.38mmol) in a mixture of THF (3ml) and 1N hydrochloric acid (1ml) was left to stand at ambient temperature for 4 days. The solvent was then evaporated to give an oil which was purified by flash chromatography (Merck 9385 silica, 10% MeOH / dichloromethane eluant) to give the title product (144mg, 80%) as a crystalline solid. MS: ESP$^+$ (M+H)$^+$=466.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.20-2.46 (m, 2H), 3.40-3.63 (m, 2H), 3.63-3.85 (m, 2H), 3.92 (dd, 1H), 4.10 (m, 1H), 4.18 (t, 1H), 4.26-4.52 (m, 4H), 4.68 (m, 1H), 4.96 (m, 1H), 5.10 (m, 1H), 5.86 (m, 1H), 6.37 (d, 1H), 7.34 (m, 2H), 8.68 (d, 2H).

Example 5: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-formyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 6 (300mg, 0.72mmol) and triethylamine (102mg, 1.01mmol) in ethyl formate (10ml) were refluxed for 12 hours, and then evaporated to give an oil which was

purified by flash chromatoraphy (Merck 9385 silica, 4% MeOH / dichloromethane eluant) to give the title product (261mg, 89%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.18 & 2.37 (2s, 2H), 3.20-3.40 (m (partially obscured), 2H), 3.57-3.66 (m, 2H), 3.92 (m, 1H), 4.05 & 4.10 (2m, 2H), 4.20 (t, 1H), 4.38-4.54 (m, 2H), 5.10 (m, 1H), 5.86 & 5.90 (2m, 1H), 6.37 (d, 1H), 7.32 (m, 2H), 8.10 & 8.18 (2s, 1H), 8.68 (d,1H). MS: ESP$^+$ (M+H)$^+$= 406.

Example 6: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-acetoxyacetyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 6 (400mg, 0.97mmol), triethylamine (205mg, 2.03mmol) and 4-(dimethylamino)pyridine (30mg) in dichloromethane (10ml) were cooled in an ice-water bath then acetoxyacetyl chloride (145mg, 1.06mmol) was added dropwise via syringe. The mixture was stirred at ice temperature for 2 hours then purified by flash chromatography (Merck 9385 silica, 2.5% MeOH / dichloromethane eluant) to give the title product (430mg, 93%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.40-2.56 (m, 2H), 3.59 (t, 1H), 3.82 (t, 1H), 3.95 (dd, 1H), 4.08 & 4.25 (2m, 2H), 4.12 (t, 1H), 4.50 (dd, 1H), 4.58 (dd, 1H), 4.74 & 4.78 (2s, 2H), 5.05 (m, 1H), 5.80 & 5.88 (2m, 1H), 6.00 (d, 1H), 7.19 (m, 2H), 8.17 (d, 1H). MS: ESP$^+$ (M+H)$^+$= 478.

Example 7: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-hydroxyacetyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Example 6 (280mg, 0.59mmol) and potassium carbonate (150mg, 1.09mmol) in MeOH (6ml) were stirred at ambient temperature for 4 hours. Water (30ml) was added to give a crystalline solid, which was filtered, washed with water and dried to give the title product (215mg, 84%). MS: ESP$^+$ (M+H)$^+$ = 436.

^{1}H-NMR (300MHz, DMSO d-6): δ = 2.22-2.42 (m, 2H), 3.52 (m, 1H), 3.68 (m, 1H), 3.92 (dd, 1H), 4.00-4.24 (m, 5H), 4.40-4.52 (m, 2H), 4.52-4.76 (m, 1H), 5.10 (m, 1H), 5.86 (m, 1H), 6.36 (d, 1H), 7.35 (m, 2H), 8.68 (d, 2H).

Reference Example 7: 5(R)-Hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

5(R)-hydroxymethyl-3-(3-fluoro-4-(4-*t*-butoxycarbonylpiperazin-1-yl)phenyl)oxazolidin-2-one (International Patent Application Publication WO 93/23384, 43.1 g, 0.11 M) was suspended by stirring in ethanol (1000 ml) under nitrogen. An ethanol solution of hydrogen chloride (3.8 M, 400 ml) was added slowly, and the mixture was stirred at ambient temperature for 18 hours. The resulting precipitate was filtered, washed with diethyl ether (3 x 250 ml), and dried, to give 5(R)-hydroxymethyl-3-(3-fluoro-4-(piperazin-1-yl)phenyl)oxazolidin-2-one hydrochloride. A further crop was obtained by evaporation of the mother liquors to give a total yield of 38.7 g.

^{1}H-NMR (300MHz, DMSO-D6) δ: 3.17 (m, 8H); 3.53 (dd, 1H); 3.64 (dd, 1H); 3.79 (dd, 1H); 4.03 (t, 1H); 4.66 (m, 1H); 7.10 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H); 9.39 (br s, 2H).
MS: ESP+ (M+H)$^+$ = 296.

5(R)-hydroxymethyl-3-(3-fluoro-4-(piperazin-1-yl)phenyl)oxazolidin-2-one hydrochloride (25 g, 75.4 mmol) was suspended by stirring in acetonitrile (700 ml) under nitrogen, and triethylamine (16.8 g, 166 mmol) added. The mixture was stirred for 10 minutes and then 2-chloro-5-cyanopyridine (10.3 g, 75.4 mmol) added, and the mixture heated under reflux for 18 hours. After cooling, the resultant solid was filtered, washed with water (3 x 500 ml) and diethyl ether (2 x 500 ml) to give 5(R)- hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one. A further crop was obtained by evaporation of the mother liquors to give a total yield of 23.2 g. MS: ESP+ (M+H)$^+$ = 398.

^{1}H-NMR (300MHz, DMSO-D6) δ: 3.03 (t, 4H); 3.54 (m, 1H); 3.63(m, 1H); 3.78 (t overlapping m, 5H); 4.03 (t, 1H); 4.66 (m, 1H); 5.18 (t, 1H); 6.97 (d, 1H); 7.07 (t, 1H); 7.20 (dd, 1H); 7.53 (dd, 1H); 7.85 (dd, 1H); 8.49 (d, 1H).

Example 8 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

Reference Example 7 (397mg, 1mmol), 3-hydroxyisoxazole (85mg, 1.1mmol) and polymer bound triphenylphosphine (3mmol/g, 416mg, 1.25mmol) were suspended with stirring in 10ml dry THF and diisopropylazodicarboxylate (242mg, 1.2mmol) added dropwise by syringe, and the mixture stirred at ambient temperature for 1hour. The mixture was filtered,

evaporated to dryness, and dissolved in EtOAc and purified by chromatography (on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 80 to 100% EtOAc in *iso*hexane) to give the title product (93 mg). MS: ESP+: $(M+H)^+ = 465$. ^{1}H-NMR (300MHz, DMSO-D6) δ: 3.06 (t, 4H); 3.80 (t, 4H); 3.87 (dd, 1H); 4.16 (t, 1H); 4.42 (dd, 1H); 4.48 (dd, 1H); 5.04 (m, 1H); 6.37 (d, 1H); 6.97 (d, 1H); 7.08 (t, 1H); 7.20 (dd, 1H); 7.51 (dd, 1H); 7.86 (dd, 1H); 8.49 (d, 1H); 8.67 (d,1H).

Example 9: 5(R)-Isothiazol-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

Diisopropylazodicarboxylate (227mg, 1.12mmol) was added dropwise, at ambient temperature, to a stirred solution of 5(R)-hydroxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one (300mg, 1.02mmol; see Example 1), 3-hydroxyisothiazole (114mg, 1.13mmol) and triphenylphosphine (304mg, 1.16mmol) in THF (8.0ml). The resulting solution was stirred at room temperature for 30 minutes before evaporating the solvent to give an orange oil. It was purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (3:2)) to give the title product (257mg, 67%) as a colourless crystalline solid. MS: ESP^+ $(M+H)^+ = 377$.
^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.45-2.55 (m, 2H), 3.94 (t, 2H), 3.98 (dd, 1H), 4.14 (t, 1H), 4.32 (m, 2H), 4.61-4.72 (m, 2H), 5.04 (m, 1H), 6.07 (m, 1H), 6.62 (d, 1h), 7.22-7.30 (m, 2H), 7.42 (dd, 1H), 8.48 (d, 1H).

Example 10: 5(R)-(1,2,5-Thiadiazol-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

A solution of 5(R)-hydroxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one (0.275g, 0.93mmol; see Example 1), 3-hydroxy-1,2,5-thiadiazole (Weinstock et al, J.Org. Chem., 32, 2823 (1967)) (0.112g,1.1mmol), and triphenylphosphine (0.288g, 1.1mmol) was stirred in dry THF (7ml) at ambient temperature and diisopropylazodicarboxylate (0.22g, 1.1mmol) in dry THF (1.0ml) added dropwise over ten minutes. After 1.5 hours, tlc (70% EtOAc/isohexane) showed essentially complete reaction. The reaction mixture was evaporated in vacuo and purified by chromatography (Merck 9385 silica, 50% EtOAc /isohexane eluant) to give the title product (256mg, 73%) as a colourless solid mp, 46-8 C.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.40 (m, 1H), 3.78 (m, 3H), 3.96 (dd, 1H), 4.20 (m, 3H), 4.64 (m, 2H), 5.10 (m,1H), 6.08 (s,1H), 7.35 (m,2H), 7.50 (d,1H), 8.41 (s,1H). MS: ESP$^+$ $(M+H)^+$ = 377.

Reference Example 8: 5(R)-(1,2,5-Thiadiazol-3-yloxymethyl)-3-phenyloxazolidin-2-one

Diisopropylazodicarboxylate (4.45g, 22mmol) was added dropwise to a stirred solution of 5(R)-hydroxymethyl-3-phenyloxazolidin-2-one (Gregory et al. J. Med. Chem., 32, 1673 (1989); 4.25g,22mmol), triphenyl phosphine (5.76g, 22mmol) and 3-hydroxy-1,2,5-thiadiazole (Weinstock et al, J.Org. Chem., 32, 2823 (1967)) (2.04g, 20mmol) in 30ml THF, in an ice-bath. After stirring at ambient temperature for two hours and evaporating in vacuo, the resulting oil was purified by chromatography (Merck 9385 silica. Gradient elution from isohexane to ca. 50% EtOAc/isohexane to give a white solid. Further purification by flash chromatography on silica using 1% MeOH/dichloromethane was necessary to remove remaining diisopropylcarboxyhydrazine yielding the title product as a white crystalline solid (4.7g, 83%). MS: ESP$^+$ $(M+H)^+$ = 278.

^{1}H-NMR (300MHz.$CDCl_3$): δ = 4.0 (dd,1H), 4.21 (t.1H), 4.6-4.77 (m, 2H), 5.04 (m,1H), 7.17 (t,1H), 7.39 (m, 2H). 7.56 (d, 2H), 8.0 (s,1H).

Reference Example 9: 5(R)-(1,2,5-Thiadiazol-3-yloxymethyl)-3-(4-iodophenyl)oxazolidin-2-one

Silver trifluoroacetate (0.727g, 3.29mmol) was added to a stirred solution of the compound of Reference Example 8 (0.70g, 2.53mmol) in chloroform/ acetonitrile (6ml/4ml) at ambient temperature. Iodine (0.67g, 2.64 mmol) was then added in portions. The resulting brown mixture was then stirred for 65h with protection from light. A yellow solid was filtered off, washing with chloroform. The filtrate and washings were evaporated in vacuo, the residue redissolved in EtOAc and washed with dilute ammonium hydroxide, water and brine. Dried over sodium sulfate and evaporated in vacuo to give a pale yellow solid on standing. Trituration with ether gave the title product as an off-white solid (0.749g, 73%).

^{1}H-NMR (300MHz, DMSO-d_6): δ = 3.95 (dd,1H), 4.19 (t,1H), 4.67 (m, 2H), 5.1 (m,1H), 7.37 (d, 2H), 7.69 (d, 2H), 8.4 (s,1H). MS: ESP+ $(M+H)^+$ = 404.

Reference Example 10 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 1 using as starting material 5(R)-hydroxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one (WO97/30995; 4.0g, 10.5mmol), 3-hydroxyisoxazole (1.0g, 11.8mmol), triphenylphosphine (3.24g, 12.4mmol) and diisopropylazodicarboxylate (2.36g, 11.7mmol) in tetrahydrofuran (60ml). Purified by flash chromatography (Merck 9385 silica; tert-butyl methyl ether / EtOAc / MeOH (70:30:0.5) eluant) to give the product (3.0g, 64%) as a colourless crystalline solid. MS: ESP$^+$ $(M+H)^+$ = 450.

Reference Example 11 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Reference Example 6 using Reference Example 10 (7.09g, 15.8mmol) and 1-chloroethyl chloroformate (2.26g, 15.8mmol) in dichloromethane (120ml) to give the product (3.71g, 59%) as a pale yellow crystalline solid. MS: ESP$^+$ $(M+H)^+$ = 360.
^{1}H-NMR (300MHz, DMSO-d6): d = 2.64 (m, 2H), 3.22-3.30 (m, 2H), 3.72 (m, 2H), 3.92 (dd, 1H), 4.21 (t, 1H), 4.40-4.55 (m, 2H), 5.10 (m, 1H), 6.02 (m, 1H), 6.38 (d, 1H), 7.32-7.44 (m, 2H), 7.52 (d, 1H), 8.68 (d, 1H), 9.30 (s(br), 2H).

Example 11 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

1,3 Dicyclohexylcarbodiimide (550mg, 2.67mmol) was added in one go at ambient temperature to a stirred solution of (S)-2,3-O-isopropylidineglyceric acid (390mg, 2.67mmol) and 1-hydroxybenzotriazole (410mg, 2.58mmol) in dichloromethane (10ml). The resulting suspension was stirred for 1hr then a further 10ml dichloromethane was added, followed by Reference Example 11 (1.0g, 2.53mmol) and N,N-diisopropylethylamine (326mg, 2.53mmol). The reaction was stirred at ambient temperature for 18hr then filtered. The filtrate was washed with water (2X) and brine then purified by flash chromatography (Merck 9385 silica; 2% MeOH in dichloromethane eluant) to give the product (754mg, 61%) as a colourless crystalline solid. MS: ESP$^+$ $(M+H)^+$ = 488.
^{1}H-NMR(300MHz, $CDCl_3$): d = 1.44 (s, 6H), 2.45-2.72 (m, 2H), 3.62-3.76 (m, 1H), 3.89-

4.05 (m, 2H), 4.10-4.20 (m, 3H), 4.24-4.38 (m,1H), 4.44-4.62 (m, 3H), 4.75 (m,1H), 5.04 (m,1H), 5.97 (m,1H), 6.00 (d, 1H), 7.25 (m, 2H), 7.45 (d,1H), 8.15 d,1H).

Example 12 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 4 using Example 11 (754mg, 1.55mmol) in a mixture of THF (15ml) and 1N hydrochloric acid (5ml). Purified by flash chromatography (Merck 9385 silica; 10% MeOH in dichloromethane eluant) to give the product (486mg, 70%) as a colourless crystalline solid, mp 140-143°C.

^{1}H-NMR (300MHz, DMSO-d6): d = 2.42 (m, 2H), 3.40-3.60 (m, 2H), 3.62-3.85 (m, 2H), 3.92 (dd, 1H), 4.10-4.30 (m, 3H), 4.30-4.56 (m, 3H), 4.79 (m, 1H), 4.94 (m, 1H), 5.09 (m, 1H), 6.00 (m, 1H), 6.37 (d, 1H), 7.28-7.44 (m, 2H), 7.50 (d, 1H), 8.66 (d, 1H).MS: ESP$^+$ (M+H)$^+$ = 448.

HPLC: Chiralpak AD (250mm x 4.6mm i.d.), 100% MeOH eluant, 1ml/min. flow rate: ret. time = 42.5 min.

Example 13 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(R)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 11 using (R)-2,3-O-isopropylidineglyceric acid (390mg, 2.67mmol), 1-hydroxybenzotriazole (410mg, 2.58mmol), dicyclohexylcarbodiimide (550mg, 2.67mmol), Reference Example 11 (1.0g, 2.53mmol) and N,N-diisopropylethylamine (326mg, 2.53mmol) in dichloromethane (20ml). Purified by flash chromatography (Merck 9385 silica; 2% MeOH in dichloromethane eluant) to give the product (682mg, 55%) as a colourless crystalline solid. MS: ESP$^+$ (M+H)$^+$ = 488.

^{1}H-NMR(300MHz, $CDCl_3$): d = 1.44 (s, 6H), 2.45-2.72 (m, 2H), 3.62-3.76 (m, 1H), 3.89-4.05 (m, 2H), 4.10-4.20 (m, 3H), 4.24-4.38 (m,1H), 4.44-4.62 (m, 3H), 4.75 (m,1H), 5.04 (m,1H), 5.97 (m,1H), 6.00 (d, 1H), 7.25 (m, 2H), 7.45 (d,1H), 8.15 d,1H).

Example 14 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 12 using Example 13 (682mg, 1.40mmol) in a mixture of THF (15ml) and 1N hydrochloric acid (5ml). Purified by flash chromatography

(Merck 9385 silica; 10% MeOH in dichloromethane eluant) to give the product (466mg, 74%) as a colourless crystalline solid: mp 136-140°C.

^{1}H-NMR (300MHz. DMSO-d6): d = 2.42 (m, 2H), 3.40-3.60 (m, 2H), 3.62-3.85 (m, 2H), 3.92 (dd, 1H), 4.10-4.30 (m, 3H), 4.30-4.56 (m, 3H), 4.79 (m, 1H), 4.94 (m, 1H), 5.09 (m, 1H), 6.00 (m, 1H), 6.37 (d, 1H), 7.28-7.44 (m, 2H), 7.50 (d, 1H), 8.66 (d, 1H). MS: ESP$^+$ (M+H)$^+$ = 448.

HPLC: Chiralpak AD (250mm x 4.6mm i.d.), 100% MeOH eluant, 1ml/min. flow rate: ret. time = 18.5 min.

Example 15 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(R)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

1,3 Dicyclohexylcarbodiimide (315mg, 1.53mmol) was added in one go at ambient temperature to a stirred mixture of Reference Example 6 (660mg, 1.45mmol), (R)-2,3-O-isopropylideneglyceric acid (240mg, 1.64mmol) and pyridine (115mg, 1.45mmol) in dichloromethane (15ml). The resulting mixture was stirred at ambient temperature for 18hr then purified by flash chromatography (Merck 9385 silica; EtOAc / isohexane (3:1) eluant) to give the product (315mg, 43%) as a colourless crystalline solid.

Example 16 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 14 using Example 15 (315mg, 0.62mmol) in a mixture of THF (6ml) and 1N hydrochloric acid (2ml). Purified by flash chromatography (Merck 9385 silica; 10% MeOH in dichloromethane eluant) to give the product (208mg, 72%) as a colourless crystalline solid: mp 128-134 °C.

^{1}NMR (300MHz, DMSO-d_6): d 2.20-2.46 (m, 2H), 3.40-3.63 (m, 2H), 3.63-3.85 (m, 2H), 3.92 (dd, 1H), 4.10 (m,1H), 4.18 (t,1H), 4.26-4.52 (m,1H), 4.68 (m,1H), 4.96 (m,1H), 5.10 (m,1H), 5.86 (m,1H), 6.37 (d,1H), 7.34 (m,2H), 8.68 (d, 2H).

MS: ESP$^+$ (M+H)$^+$ = 466.

HPLC: Chiralpak AD (250mm x 4.6mm i.d.), 100% MeOH eluant, 1ml/min. flow rate: ret. time = 11.2min.

Example 17 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 15 using 1,3 dicyclohexylcarbodiimide (315mg, 1.53mmol). Reference Example 6 (660mg, 1.45mmol), (S)-2,3-O-isopropylidineglyceric acid (240mg, 1.64mmol) and pyridine (115mg, 1.45mmol) in dichloromethane (15ml). Purified by flash chromatography (Merck 9385 silica; EtOAc / isohexane (3:1) eluant) to give the product (282mg, 38%) as a colourless crystalline solid. MS: ESP$^+$ (M+H)$^+$ = 506.

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.32 (s, 3H), 1.34 (s, 3H), 2.25-2.50 (m, 2H), 3.63-3.87 (m, 2H), 3.95 (dd, 1H), 4.02-4.32 (m, 4H), 4.43-4.55 (m, 2H), 4.92 (m, 1H), 5.12 (m, 1H), 5.89 (m, 1H), 6.37 (d, 1H), 7.35 (d, 2H), 8.68 (d, 1H).

Example 18 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 16 using Example 17 (282mg, 0.56mmol) in a mixture of THF (6ml) and 1N hydrochloric acid (2ml). Purified by flash chromatography (Merck 9385 silica; 10% MeOH in dichloromethane eluant) to give the product (183mg, 70%) as a colourless crystalline solid: mp 136-142 °C.

^{1}NMR (300MHz, DMSO-d_6): d 2.20-2.46 (m, 2H), 3.40-3.63 (m, 2H), 3.63-3.85 (m, 2H), 3.92 (dd, 1H), 4.10 (m,1H), 4.18 (t,1H), 4.26-4.52 (m,1H), 4.68 (m,1H), 4.96 (m,1H), 5.10 (m,1H), (m,1H), 6.37 (d,1H), 7.34 (m,2H), 8.68 (d, 2H).

MS: ESP$^+$ (M+H)$^+$ = 466.

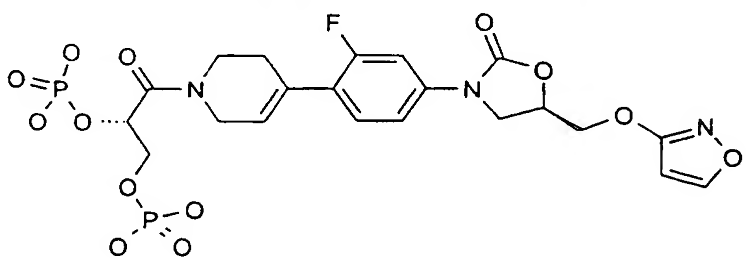
HPLC: Chiralpak AD (250mm x 4.6mm i.d.), 100% MeOH eluant, 1ml/min. flow rate: ret. time = 38.4 min.

Reference Example 12: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-di-(di-t-butoxyphosphoryl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Di-tert-butyl N,N diethylphosphoramidite (1.67g, 6.24mmol) was added dropwise at room temperature, under an atmosphere of nitrogen, to a stirred suspension of Example 12 (1.0g, 2.24mmol) and 1H-tetrazole (1.4g, 20.0mmol) in tetrahydrofuran (40ml). The resulting mixture was stirred for 2hr. then cooled to -40°C and treated portionwise with 3-chloroperoxybenzoic acid (1.9g 60% strength, 6.6mmol). The reaction was stirred at -40 to -

20°C for 1hr. then diluted with EtOAc (150ml), washed succesively with 10% aqueous sodium bisulfite solution, sat. sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated to give a colourless oil.Purified by flash chromatography (Merck 9385 silica, 20-30% acetonitrile / EtOAc) to give the product (625mg, 34%) as a colourless foam. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.48 (m, 36H), 2.45-2.70 (m, 2H), 3.58-3.71 & 3.73-3.86 (m, 1H), 3.92-4.10 (m, 2H), 4.10-4.38 (m, 5H), 4.47-4.62 (m, 2H), 4.97-5.08 (m, 1H), 5.22-5.32 (m, 1H), 5.88 (m, 1H), 6.02 (d, 1H), 7.18-7.28 (m, 2H), 7.43 (d, 1H), 8.16 (d, 1H). MS: ESP$^+$ $(M+H)^+$ = 832.

Example 19: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-diphosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one



A 4M solution of HCl in dioxane (6ml) was added in one go at room temperature to a stirred solution of Reference Example 12 (600mg, 0.72mmol) in dioxane (6ml). The resulting yellow mixture was stirred 1hr. then concentrated under reduced pressure. Trituration with diethyl ether gave a yellow solid which was filtered, washed with ether, dried and then dissolved in water and lyophilized to a pale yellow solid (435mg).

^{1}H-NMR (300MHz, DMSO-d6 + CD_3COOD): δ = 2.35-2.50 (m, 2H), 3.52-3.68 & 3.70-3.85 (m, 2H), 3.90 (dd, 1H), 4.05-4.35 (m, 5H), 4.35-4.53 (m, 2H), 5.05 (m, 1H), 5.10-5.25 (m, 1H), 5.98 (m, 1H), 6.25 (d, 1H), 7.25-7.40 (m, 2H), 7.45 (dd, 1H), 8.54 (d, 1H). MS: ESP$^+$ $(M+H)^+$ = 608.

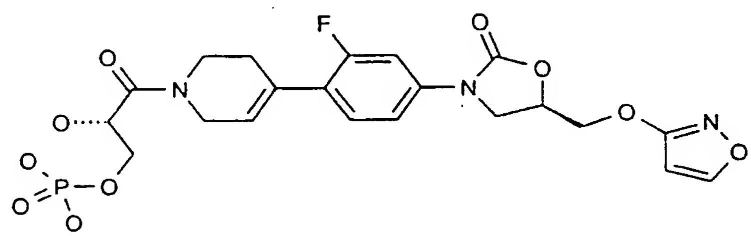
Reference Example 13: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(di-t-butoxyphosphoryl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

To a stirred solution of the starting material Example 12 (600mg, 1.34mmol) and 1H-tetrazole (310mg, 4.43mmol) in THF (30ml) under nitrogen was added di-tert-butyl N,N diethylphosphoramidite (368mg, 1.48mmol) over a few minutes. After stirring for 90 minutes

the solution was cooled to -40^{0}C and 3-chloroperoxybenzoic acid (425mg 60% strength, 1.48mmol) added in portions. The reaction mixture was allowed to warm to ambient temperature and stirred for 30 minutes. EtOAc was added, the solution washed with sodium metabisulfite, sodium bicarbonate and brine solutions, the organic phase dried over anhydrous magnesium sulfate and evaporated in vacuo. The crude product was purified by flash chromatography (Merck 9385 silica, 10-20% acetonitrile / EtOAc) to give the title compound (165mg, 19%) as a colourless gum.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.48 (s, 9H), 1,50 (s, 9H), 2.45-2.80 (m, 2H), 3.61-3.86 (m, 2H), 3.96 (dd, 1H), 4.02-4.12 (m, 3H), 4.16 (t, 1H), 4.22-4.30 (m, 2H), 4.47-4.61 (m, 2H), 4.64-4.77 (m, 1H), 5.03 (m, 1H), 6.00 (m, 1H), 6.03 (d, 1H), 7.20-7.30 (m, 2H), 7.46 (d, 1H), 8.16 (d, 1H). MS: ESP$^+$ (M+H)$^+$ = 640.

Example 20: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one



TFA (2ml) was added dropwise at room temperature to a stirred solution of Reference Example 13 (165mg, 0.26mmol) in dichloromethane (8ml). The resulting yellow solution was stirred 30 min. then evaporated under reduced pressure to a yellow foam. Trituration with diethyl ether gave the title compound (120mg) as a yellow solid.

^{1}H-NMR (300MHz, DMSOd6 + CD_3COOD): δ = 2.30-2.50 (m, 2H), 3.50-3.65 & 3.65-3.82 (m, 2H), 3.92 (dd, 1H), 3.97-4.40 (m, 5H), 4.40-4.62 (m, 3H), 5.05 (m, 1H), 6.00 (m, 1H), 6.28 (d, 1H), 7.25-7.43 (m, 2H), 7.48 (d, 1H), 7.57 (d, 1H).

MS: ESP$^+$ (M+H)$^+$ = 528.

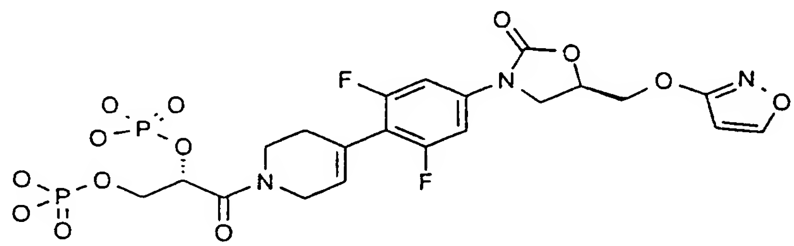
Reference Example 14: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-di-(di-t-butylphosphoryl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The title compound was prepared, with only non-critical variations, by the method for Reference Example 12 on a 4.3mM scale, using as starting material Example 18.

Yield = 1.86g (51%).

NMR (300Mz. DMS0-d6): δ 1.42 (s, 36H), 2.5 (m, partially obscured), 3.3 - 3.9 (m, 4H), 3.94 (d of d. 1H), 4.1 (s, 2H), 4.21 (t, 1H), 4.48 (m, 2H), 5.14 (m, 2H), 5.90 (s, 1H), 6.38 (s, 1H), 7.37 (d, 2H), 8.70 (s, 1H). MS: ESP+ (M+H)=850.

Example 21: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-diphosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one



The title compound was prepared, with only non-critical variations, by the method for Example 19 on a 1.4mM scale, using as starting material Reference Example 14.

Yield = 735mg (98%).

NMR (300Mz. DMS0-d6): δ = 2.5 (m, partially obscured), 3.57 & 3.77 (2m, 2H), 3.91 (d of d, 1H), 4.0 - 4.4 (m, 4H), 4.18 (t, 1H), 4.58 (m, 2H), 5.1 (m, 2H), 5.85 (s, 1H), 6.36 (s, 1H), 7.35 (d, 2H), 8.78 (s, 1H). MS: ESP+ (M+H)=626.

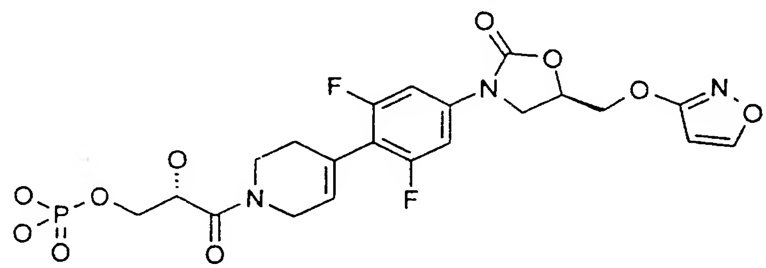
Reference Example 15: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(di-t-butylphosphoryl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred solution of the starting material Example 18 (1.02g, 2.2mmol) and tetrazole (462mg, 6.6mg) in THF (30ml) at ambient temperature under nitrogen, was added di-tert-butyl N,N diethylphosphoramidite (575mg, 2.31mmol) over ~2 minutes. After stirring for 90 minutes the solution was cooled to -40°C and m-chloroperbenzoic acid (2.5mmol. 480mg of 90% strength) was added in portions. The reaction mixture was allowed to warm to ambient

temperature and stir for 30 minutes. EtOAc was added and the mixture was washed with aqueous sodium metabisulfite, saturated sodium bicarbonate and brine solutions. The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The title compound was isolated by MPLC (EtOAc) as a brittle glass (406mg, 28%). MS : ESP+ (M+H) = 658; ESP- (M-H) = 656.

NMR (300Mz, DMS0-d6): δ 1.42 (s, 18H), 2.5 (m, partially obscured), 3.55 - 3.95 (m, 4H), 3.95 (d of d, 1H), 4.0 - 4.15 (m, 2H), 4.25 (t, 1H), 4.50 (m, 2H), 4.63 (m, 1H), 5.14 (m, 1H), 5.54 (d, 1H), 5.91 (s, 1H), 6.40 (s, 1H), 7.37 (d, 2H), 8.70 (1H, s).

Example 22: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one



To a stirred solution of the starting material Reference Example 15 (100mg, 0.15mmol) in dioxan (1ml) was added 4M HCl / dioxan (3ml). The solution was stirred at ambient temperature for 30 mins. and then evaporated. The residue was triturated well with ether giving the title compound as a white powder (80mg, 96%).

NMR (300Mz, DMS0-d6): 2.43 (m, partially obscured), 3.6 - 4.35 (m, 8H), 4.35 - 4.60 (m, 3H), 5.09 (m, 1H), 5.85 (s, 1H), 6.30 (s, 1H), 7.31 (d, 2H), 8.60 (s, 1H).

MS: ESP+ (M+H) = 546.

Example 23: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(cyclo-2(S),3-diphosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred partial solution of the starting material Example 21 (100mg, 0.16mmol) in THF (8ml) was added dicyclohexyl carbodiimide (40mg, 0.195mmol). DMF(4ml) was added to give a clear solution. After stirring for 18hrs at ambient temperature, more DCCI (40mg, 0.195mmol) was added. The reaction was essentially complete by HPLC (Partisil SAX 10μ column, 0.0M to 0.3M pH6.5 phosphate buffer gradient) after a further 3hrs. The solvent was evaporated and the residue was taken into water and filtered. The filtrate was

chromatographed by MPLC (0 -25% acetonitrile / water gradient on Mitsubishi HP20SS polystyrene resin) and the title compound was obtained by freeze drying after partial evaporation to remove acetonitrile.

Yield = 49mg (50%). MS : ESP- (M-H) = 606.

NMR (300Mz, DMS0-d6): δ = 2.4 (m, partially obscured), 3.7 - 4.0 (m, 3H), 4.18 (m, 4H), 4.48 (m. 3H), 5.05 (m, 1H), 5.19 & 5.30 (2m, 1H), 5.85 (s, 1H), 6.30 (s, 1H), 7.31(d, 2H), 8.59 (s, 1H).

Example 24: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(4-hydroxybutanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 6 (0.223 g, 0.54 mmol), 4-hydroxybutyric acid sodium salt (0.082 g, 0.65 mmol) and HOBT (0.087 g, 0.65 mmol) in *DMF* (5 ml) was added EDC (0.124 g, 0.65 mmol). The mixture was stirred for 4 days and then evaporated. The residue was purified by MPLC [5% MeOH/CH_2Cl_2 as eluant] to give after trituration with diethyl ether, as a white solid (0.141 g, 56%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.63 (m, 2H), 2.29 (m, 1H), 2.38 (m, 2H), 3.25 (d, 1H), 3.40 (m, 2H), 3.62 (m. 2H), 3.91 (dd, 1H), 4.10 (d, 1H), 4.19 (t, 2H), 4.44 (m. 3H), 5.09 (m, 1H), 5.84 (s. 1H), 6.38 (d. 1H), 7.36 (d, 2H) and 8.70 (d, 1H).

MS: ESP$^+$ (M+H)$^+$ = 464.

Example 25: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(4-methoxybutanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 6 (0.285 g, 0.69 mmol), 2-(2-methoxyethoxy)acetic acid (0.111 g, 0.83 mmol), triethylamine (0.070 g, 0.096 ml, 0.69 mmol) and HOBT (0.112 g. 0.83 mmol) in dichloromethane (5 ml) was added EDC (0.159 g, 0.83 mmol). The mixture was stirred for 17h and then the solution was washed with water (10 ml), dried and evaporated. The residue was purified by MPLC [3% MeOH/CH_2Cl_2 as eluant] to give a colourless oil (0.201 g, 61%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.36 (d, 2H), 3.25 (s, 3H), 3.45 (m, 2H), 3.59 (m, 4H), 3.92 (dd, 1H). 4.09 (m. 2H). 4.18 (m. 3H), 4.45 (m, 2H), 5.09 (m, 1H), 5.86 (s, 1H), 6.38 (d. 1H), 7.35 (d. 2H) and 8.69 (d. 1H).

Reference Example 16: 6-Hydroxymethyl-2-phenyl-1,3-dioxane

(D,L)-Malic acid (5.0 g, 37 mmol) in dry THF (25 ml) under nitrogen was treated with trimethyl borate (12.5 ml) and borane-dimethylsulfide (2.0M in THF) (60 ml, 120 mmol) dropwise at 0 °C. After the addition was complete stirring was continued at 0 °C for 5min. During which time a white precipitate formed. The ice-bath was removed and stirring continued overnight. After 17h the solution was slowly treated with MeOH (30 ml) and then evaporated. The residue was purified by MPLC [10% MeOH/CH_2Cl_2 as eluant] to give the triol (3.57 g). This was dissolved in benzaldehyde (150ml) containing tosic acid (0.64 g, 3.37 mmol) and stirred for 60h and then evaporated. The residue was dissolved in dichloromethane, washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated. The residue was was purified by MPLC [20→45% EtOAc/hexanes eluant] to give the product as an oil (1.47 g, 22%). MS: ESP^+ $(M+H)^+$ = 195.

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.50 (d, 1H), 1.62 (ddd, 1H), 3.38 (dd, 1H), 3.48 (dd, 1H), 3.90 (m, 2H), 4.14 (dd, 1H), 4.70 (t, 1H), 5.49 (s, 1H) and 7.38 (m, 5H).

Reference Example 17: 6-Carboxy-2-phenyl-1,3-dioxane

To a stirred solution of the alcohol Reference Example 16 (1.47 g, 7.60 mmol) in aqueous sodium hydroxide (7.60 mmol, 0.304 g in 30 ml) at 0°C was added potassium permanganate (1.80 g, 11.4 mmol) portionwise. After 3.5h the mixture was filtered and acidified to pH 2. The solution was saturated with sodium chloride and extracted with EtOAc (4 x 50 ml), dried and evaporated to a residue. This white solid was dissolved in dichloromethane and extracted with ammonium hydroxide (2 x 15 ml). The basic extracts were acidified at 0 °C to pH 2 with conc. hydrochloric acid, and the acidic mixture extracted with dichloromethane (2 x 50 ml). The organics were dried and evaporated to give the acid as a gum (0.15 g, 10%). MS: ESP^+ $(M+H)^+$ = 209.

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.82 (m, 2H), 3.96 (m, 1H), 4.18 (dd, 1H), 4.50 (dd, 1H), 5.58 (s, 1H), 7.40 (m, 5H) and 12.82 (s, 1H).

Example 26: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-phenyl-1,3-dioxan-4(R,S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 6 (0.220 g, 0.53 mmol), Reference Example 17 (0.133 g, 0.64 mmol), triethylamine (0.054 g, 0.074 ml, 0.53 mmol) and HOBT (0.086 g, 0.64

mmol) in dichloromethane (6 ml) was added EDC (0.123 g, 0.64 mmol). The mixture was stirred for 60h and then the solution was washed with 2N HCL (10 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [4% MeOH/CH_2Cl_2 as eluant] to give an oil (0.246 g, 82%). MS: ESP$^+$ $(M+H)^+$ = 568.

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.59 (d, 1H), 2.10 (m, 1H), 2.33 (m, 2H), 3.55 (m, 1H), 3.78 (m, 1H), 3.90 (dd, 1H), 4.07 (m, 2H), 4.15 (m, 3H), 4.45 (m, 2H), 4.90 (m, 1H), 5.10 (m, 1H), 5.71 (d, 1H), 5.88 (s, 1H), 6.38 (d, 1H), 7.38 (m, 7H) and 8.70 (d, 1H).

Reference Example 18: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxycarbonylamino-2(R,S)-hydroxy-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 6 (0.091 g, 0.22 mmol), (D,L)-*N*-BOC-isoserine (0.054 g, 0.27 mmol), triethylamine (0.022 g, 0.031 ml, 0.22 mmol) and HOBT (0.036 g, 0.27 mmol) in dichloromethane (3 ml) was added EDC (0.052 g, 0.27 mmol). The mixture was stirred for 18h and then the solution was washed with 2N HCL (10 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [3% MeOH/CH_2Cl_2 as eluant] to give the product as a tan solid (0.047 g, 38%).

MS: ESP$^+$ $(M+H)^+$ = 565.

Example 27: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-amino-2(R,S)-hydroxy-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 18 (0.047 g, 0.083 mmol) was dissolved in EtOAc (3 ml) saturated with hydrogen chloride and stirred for 18h. The solution was evaporated and triturated with EtOAc to give the product as an off-white solid (0.034 g, 88%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.30 (d, 2H), 3.70 (m, 2H), 3.90 (dd, 1H), 45.19 (m, 4H), 4.44 (m, 2H), 4.60 (m, 1H), 5.10 (m, 1H), 5.90 (s, 1H), 6.37 (d, 1H), 7.30 (s, 1H), 7.38 (s, 1H), 7.89 (s, 3H) and 8.69 (d, 1H). MS: ESP$^+$ $(M+H)^+$ = 465.

Example 28: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-phenyl-1,3-dioxan-5(R,S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 6 (0.344 g, 0.83 mmol), 5-carboxy-2-phenyl-1,3-dioxan (JOC, 1997, 62, 4029) (0.208 g, 1.00 mmol), triethylamine (0.084 g, 0.116 ml, 0.83

mmol) and HOBT (0.135 g, 0.1.00 mmol) in dichloromethane (10 ml), was added EDC (0.192 g, 1.00 mmol). The mixture was stirred for 24h and then the solution was washed with 2N HCL (10 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [2% MeOH/CH_2Cl_2 as eluant] to give the product as an oil (0.357 g, 76%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.38 (d, 2H), 2.99 (s, 1H), 3.70 (d, 2H), 3.90-4.55 (m, 10H), 5.10 (m, 1H), 5.55 (s, 1H), 5.90(s, 1H), 6.37 (d, 1H), 7.40 (m, 7H) and 8.68 (d, 1H).
MS: ESP$^+$ (M+H)$^+$ = 568

Example 29: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-hydroxy-2-hydroxymethyl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Example 28 (0.155 g, 0.27 mmol) in dichloromethane (4 ml) at 0 °C was treated with boron trichloride-dimethyl sulfide (2.0M in CH_2Cl_2) (0.40 ml, 0.81 mmol) for 4.5h. MeOH (1 ml) was added until all solids had dissolved. The solution was then evaporated and the residue purified by MPLC [6% MeOH/CH_2Cl_2] as eluant] to give after trituration with diethyl ether, a white solid (0.025 g, 19%). MS: ESP$^+$ (M+H)$^+$ = 480.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.40 (d, 2H), 3.15 (m, 1H), 3.40 (m, 6H), 3.79 (d, 2H), 3.98 (dd, 1H), 4.19 (s, 1H), 4.26 (dd, 1H), 4.34 (s, 1H), 4.51 (m, 2H), 5.15 (m, 1H), 5.93 (m, 1H), 6.43 (d, 1H), 7.40 (s, 1H), 7.44 (s, 1H) and 8.74 (d, 1H).

Example 30: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,3-propenoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Acryloyl chloride (0747 g, 0.67 ml, 8.25 mmol) in dichloromethane (5 ml) at 0 °C was treated with Reference Example 6 (0.682 g, 1.65 mmol) in dichloromethane (5 ml) containing DMAP (0.201 g, 1.65 mmol) and triethylamine (0.333 g, 0.46 ml, 3.39 mmol). The solution was stirred for 1.5h. The solution was washed with 2N HCL (10 ml), saturated aqueous sodium hydrogen carbonate (10 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [2% MeOH/CH_2Cl_2 as eluant] to give a white solid (0.471 g, 66%). MS: ESP$^+$ (M+H)$^+$ = 432.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.40 (d, 2H), 3.80 (d, 2H), 3.99 (dd, 1H), 4.25 (m, 3H), 4.54 (m, 2H), 5.16 (m, 1H), 5.75 (d, 1H), 5.93 (s, 1H), 6.20 (d, 1H), 6.45 (s, 1H), 6.88 (m, 1H), 7.42 (s, 1H), 7.48 (s, 1H) and 8.75 (d, 1H).

Reference Example 19 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,3(R,S)-epoxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

n-Butyllithium (1.6M in hexanes) (0.65 ml, 1.04 mmol) was added to a solution of *tert*-butylhydroperoxide (5.5M in decane) (0.26 ml, 1.43 mmol) in THF (5 ml) at -78 °C. The mixture was stirred for 5 min. A solution of the acrylamide, Example 30 (0.408 g, 0.95 mmol) in dry THF (2 ml) was added and stirring continued with the ice-bath removed until the temperature reached *ca.* 0 °C whereupon a water ice-bath was put in place. Solid sodium sulfite (0.080 g, 0.30 mmol) was added and stirring continued for 15min. Dichloromethane (10 ml) was added and the mixture filtered through Celite and then evaporated. The residue was purified by MPLC [2% $MeOH/CH_2Cl_2$ as eluant] to give the product as a gum (0.378 g, 89%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.46 (d, 2H), 2.87 (m, 1H), 3.00 (m, 1H), 3.67-4.04 (m, 4H), 4.17 (s, 1H), 4.27 (t, 1H), 4.40 (d, 1H), 4.52 (m, 2H), 5.16 (m, 1H), 5.95 (s, 1H), 6.43 (s, 1H), 7.40 (s, 1H), 7.45 (s, 1H) and 8.76 (d, 1H).

MS: ESP$^+$ (M+H)$^+$ = 448.

Example 31: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-morpholinopropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 19 (0.073 g, 0.16 mmol) and morpholine (0.014 g, 0.014 ml, 0.16 mmol) were refluxed in isopropanol (1 ml) for 1h. and then heated at 50 °C for 2h. The solution was allowed to cool to RT overnight and then evaporated. The residue was purified by MPLC [4% $MeOH/CH_2Cl_2$ as eluant] to give a white foam (0.056 g, 66%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.41 (d, 2H), 2.60 (m, 6H), 3.60 (d, 4H), 3.78 (m, 2H), 4.00 (dd, 1H), 4.17 (s, 1H), 4.26 (dd, 1H), 4.34 (s, 1H), 4.56 (m, 3H), 5.04 (dd, 1H), 5.15 (m, 1H), 5.94 (s, 1H), 6.43 (d, 1H), 7.40 (s, 1H), 7.44 (s, 1H) and 8.74 (s, 1H). MS: ESP$^+$ (M+H)$^+$ = 535.

Reference Example 20: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-(2-tert-butyldimethylsilyloxypyrrolidin-1-yl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Reference Example 19 (0.149 g, 0.333 mmol) and 2-*tert*-butyldimethylsilyloxy pyrrolidine (0.067 g, 0.333 mmol) in isopropanol (3 ml) were heated at 60 °C until TLC indicated completion. The solution was evaporated and the residue was purified by MPLC [3→10% MeOH/CH_2Cl_2 as eluant] to give a colourless gum (0.173 g, 80%). MS: ESP^+ $(M+H)^+$ = 649. ^{1}H-NMR (300MHz, DMSO-d6): δ = 0.00 (s, 6H), 0.82 (s, 9H), 1.50 (m, 1H), 1.98 (m, 1H), 2.23-2.95 (m, 8H), 3.71 (s, 2H), 3.90 (dd, 1H), 4.08 (s, 1H), 4.17 (t, 1H), 4.30 (s, 2H), 4.45 (m, 3H), 5.03 (m, 2H), 5.83 (s, 1H), 6.33 (d, 1H), 7.30 (s, 1H), 7.34 (s, 1H) and 8.64 (s, 1H).

Example 32: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-(2-hydroxypyrrolidino)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The silyl ether Reference Example 20, (0.169 g, 0.26 mmol) in dry THF (5 ml) at 0 °C was treated with tetrabutylammonium flouride (1.0M in THF) (0.52 ml, 0.52 mmol) and then stirred for 5h. The solution was evaporated and the residue was purified by MPLC [3→6% MeOH/CH_2Cl_2 as eluant] to give a white solid(0.104 g, 75%).
^{1}H-NMR (300MHz, DMSO-d6): δ = 1.54 (s, 1H), 1.92 (m, 1H), 2.30 (m, 3H), 2.50-2.88 (m, 5H), 3.63 (m, 2H), 3.89 (dd, 1H), 4.13 (m, 4H), 4.45 (m, 3H), 4.65 (s, 1H), 5.05 (m, 2H), 5.86 (s, 1H), 6.35 (d, 1H), 7.34 (s, 1H), 7.38 (s, 1H) and 8.68 (d, 1H).
MS: ESP^+ $(M+H)^+$ = 535.

Reference Example 21: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-phenyl-1,3-dioxan-5(R,S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)-oxazolidin-2-one

To a stirred solution of Reference Example 11 (0.368 g, 0.93 mmol) the acid, 5-carboxy-2-phenyl-1,3-dioxan (JOC, 1997, **62**, *4029*) (0.232 g, 1.12 mmol), triethylamine (0.094 g, 0.129 ml, 0.93 mmol) and HOBT (0.151 g, 1.12 mmol) in dichloromethane (11 ml) was added EDC (0.215 g, 1.12 mmol). The mixture was stirred for 20h and then the solution was washed with 2N HCL (10 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [2% MeOH/CH_2Cl_2 as eluant] to give an oil (0.475 g, 93%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.62 (m, 2H), 3.48 (m, 1H), 3.70 (m, 1H), 3.82 (m, 1H), 3.93-4.60 (m, 10H), 5.14 (m, 1H), 5.60 (s, 1H), 6.08 (s, 1H), 6.42 (d, 1H), 7.46 (m, 8H) and 8.76 (d, 1H). MS: ESP$^+$ $(M+H)^+$ = 550.

Example 33: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-hydroxy-2-hydroxymethyl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Reference Example 21(0.475 g, 0.87 mmol) was stirred in 80% acetic acid/water (10 ml) for 24h. The precipitate slowly dissolved. The solution was evaporated and purified by MPLC [5% $MeOH/CH_2Cl_2$ as eluant] to give after trituration with diethyl ether, a white powder (0.284 g, 71%). MS: ESP$^+$ $(M+H)^+$ = 462.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.51 (d, 2H), 3.15 (m, 1H), 3.58 (m, 4H), 3.78 (m, 2H), 3.99 (dd, 1H), 4.26 (d, 2H), 4.28 (t, 1H), 4.54 (m, 2H), 4.65 (m, 2H), 5.15 (m, 1H), 6.06 (s, 1H), 6.43 (d, 1H), 7.35-7.63 (m, 3H) and 8.76 (d, 1H).

Reference Example 22: 5(R,S)-Carboxymethyl-2,2-dimethyl-4-oxo-1,3-dioxolane

(D,L)-Malic acid (12.41 g, 92.6 mmol) and PTSA (2.32 g, 9.26 mmol) in 2,2-dimethoxypropane (35 ml) were stirred for 5 days. The solution was evaporated and the residue was purified by MPLC [25% EtOAc/isohexane as eluant] to give a colurless gum (11.48 g, 71%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.58 (s, 3H), 1.60 (s, 3H), 2.82 (m, 2H), 4.85 (t, 1H) and 12.64 (s, 1H).

Example 34: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5(R,S)-ylacetyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)-oxazolidin-2-one

To a stirred solution of Reference Example 11 (0.384 g, 0.97 mmol), the acid (Reference Example 22) (0.203 g, 1.17 mmol), triethylamine (0.098 g, 0.135 ml, 0.97 mmol) and HOBT (0.158 g, 1.17 mmol) in dichloromethane (11 ml) was added EDC (0.225 g, 1.17 mmol). The mixture was stirred for 60h and then the solution was dried and evaporated. The residue was purified by MPLC [3% $MeOH/CH_2Cl_2$ as eluant] to give an oil (0.356 g, 71%). MS: ESP$^+$ $(M+H)^+$ = 516.

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.57 (s, 3H), 1.60 (s, 3H), 2.53 (d, 2H), 3.02 (m, 2H), 3.70 (m, 2H), 4.00 (dd, 1H), 4.19 (d, 2H), 4.25 (t, 1H), 4.52 (m, 2H), 4.89 (t, 1H), 5.15 (m, 1H), 6.05 (s, 1H), 6.44 (d, 1H), 7.36-7.63 (m, 3H) and 8.75 (d, 1H).

Example 35: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-carboxy-3(R,S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Example 34 (0.345 g, 0.67 mmol) was stirred in 80% acetic acid/water (5 ml) for 20h. The acetonide slowly dissolved and then the product slowly precipitated. Diethyl ether (10 ml) was added and the solid collected by filtration to give a white solid (0.300 g, 94%). MS: ESP$^-$ (M-H)$^-$ = 474.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.52 (d, 2H), 2.80 (m, 2H), 3.71 (s, 2H), 4.00 (dd, 1H), 4.20 (d, 2H), 4.28 (t, 1H), 4.41 (t, 1H), 4.55 (m, 2H), 5.15 (m, 1H), 6.08 (s, 1H), 6.46 (d, 1H), 7.35-7.62 (m, 3H) and 8.77 (d, 1H).

Reference Example 23: 5(R,S)-Methylaminocarbonylmethyl-2,2-dimethyl-4-oxo-1,3-dioxolane

The acid Reference Example 22 (2.84 g, 16.32 mmol) was heated under reflux in thionyl chloride (25 ml) for 1.25h under nitrogen. The solution was evaporated and azeotroped with toluene (2 x). A portion of the crude acid chloride (5.44 mmol) was dissolved in dichloromethane (5 ml), treated with methylamine (2.0M in THF) (5.44 ml, 10.88 mmol) and stirred for 1.5h. The resultant suspension was diluted, washed with 2N HCL (10 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [5% MeOH/CH_2Cl_2 as eluant] to give a pale tan solid (0.393 g, 39%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.56 (s, 6H), 2.66 (m, 2H), 2.68 (s, 3H), 4.82 (t, 1H) and 7.95 (s, 1H), MS: ESP$^+$ (M+H)$^+$ = 188.

Reference Example 24: 2(R,S)-hydroxy-3-methylaminocarbonylpropanoic acid

The amide Reference Example 23 (0.392 g, 2.10 mmol) was stirred in MeOH (4 ml) containing PTSA (0.053 g, 0.21 mmol) for 5 days. The solution was evaporated and the residue was purified by MPLC [5% MeOH/CH_2Cl_2 as eluant] to give the methyl ester (0.284 g). This was dissolved in MeOH/water (3:1) (4 ml), treated with lithium hydroxide (0.370 g, 8.82 mmol) and stirred for 15min. The mixture was diluted with water (20 ml), treated with

Dowex 50W-X8(H), stirred for 5min, filtered and evaporated to in vacuo to give a gum (0.216 g, 83%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.38 (dd, 1H), 2.49 (dd, 1H), 2.64 (s, 3H), 3.54 (br s, 1H), 4.34 (m, 1H), 7.87 (m, 1H) and 12.53 (br s, 1H). MS: ESP$^-$ (M-H)$^-$ = 146.

Example 36: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-methylaminocarbonylpropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 11 (0.175 g, 0.44 mmol), the acid Reference Example 24 (0.078 g, 0.53 mmol), triethylamine (0.044 g, 0.061 ml, 0.44 mmol) and HOBT (0.072 g, 0.53 mmol) in dichloromethane (6 ml) was added EDC (0.102 g, 0.53 mmol). The mixture was stirred for 16h. TLC indicated incomplete reaction and more acid (0.138 g, 0.94 mmol), HOBT (0.127 g, 0.94 mmol) and EDC (0.180 g, 0.94 mmol) was added. After 5h the solution was evaporated. The residue was purified by MPLC [5→15% MeOH/CH_2Cl_2 as eluant] to give an oil (0.070 g, 33%). MS: ESP$^+$ (M+H)$^+$ = 489.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.44 (m, 4H), 2.63 (d, 3H), 3.66 (m, 1H), 3.77 (s, 1H), 4.00 (dd, 1H), 4.22 (m, 3H), 4.54 (m, 2H), 4.79 (m, 1H), 5.15 (m, 1H), 5.38 (d, 1H), 6.10 (s, 1H), 6.48 (d, 1H), 7.35-7.64 (m, 3H), 7.88 (s, 1H) and 8.79 (d, 1H).

Example 37: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3(R,S)-hydroxy-3-methylaminocarbonylpropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

To a stirred solution of Example 35 (0.070 g, 0.15 mmol) and HOBT (0.020 g, 0.15 mmol) in dichloromethane (4 ml) was added EDC (0.028 g, 0.15 mmol) and then methylamine (2.0M in THF) (0.23 ml, 0.45 mmol). The mixture was stirred for 22h and then purified by MPLC [5% MeOH/CH_2Cl_2 as eluant] to give after trituration with diethyl ether a white solid (0.01g, 14%).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.48 (d, 2H), 2.65 (d, 3H), 2.69 (m, 2H), 3.69(m, 2H), 3.94 (dd, 1H), 4.17 (m, 2H), 4.20 (t, 1H), 4.30 (m, 1H), 4.48 (m, 2H), 5.08 (m, 1H), 5.61 (m, 1H), 6.00 (s, 1H), 6.39 (d, 1H), 7.38 (m, 2H), 7.50 (d, 1H), 7.78 (m, 1H) and 8.70 (d, 1H). MS: ESP$^+$ (M+H)$^+$ = 489.

Reference Example 25: 5(R,S)-(2-(2-Methoxyethoxy)ethoxy)carbonylmethyl-2,2-dimethyl-4-oxo-1,3-dioxolane

The acid (Reference Example 22) (2.75 g, 15.80 mmol) in dichloromethane (15 ml) at 0 °C was treated with oxalyl chloride (2.99 g, 2.1 ml, 23.71 mmol) and stirred with a drop of *DMF* for 2h. The solution was evaporated. A portion of the crude acid chloride (1.90 g, 9.84 mmol) in dichloromethane (20 ml) at 0 °C containing 4-DMAP (1.20 g, 9.84 mmol) was treated with 2-(2-methoxyethoxy)ethanol (4.72 g, 4.70 ml, 39.36 mmol) and stirred overnight. The solution was washed with 2N HCL (2 x 15 ml), brine (10 ml), dried and evaporated. The residue was purified by MPLC [3% MeOH/CH_2Cl_2 as eluant] to give an oil (0.785 g, 29%).
^{1}H-NMR (300MHz, DMSO-d6): δ = 1.54 (s, 6H), 2.89 (t, 2H), 3.27 (s, 3H), 3.43 (m, 2H), 3.53 (m, 2H), 3.60 (m, 2H), 4.19 (m, 2H) and 4.84 (t, 1H).

Reference Example 26: 2(R,S)-Hydroxy-3-(2-(2-methoxyethoxy)ethoxy)carbonyl-propanoic acid

Reference Example 25 (0.785 g, 2.84 mmol) was stirred in 80% acetic acid/water (5 ml) for 5 days. The solution was evaporated to give an orange oil (0.600 g, 89%).
^{1}H-NMR (300MHz, DMSO-d6): δ = 2.54 (dd, 1H), 2.72 (dd, 1H), 3.26 (s, 3H), 3.42 (m, 2H), 3.52 (m, 2H), 3.59 (m, 2H), 4.13 (m, 2H), 4.30 (m, 1H), 5.49 (s, 1H) and 12.58 (s, 1H). MS: ESP$^-$ (M-H)$^-$ = 235.

Example 38: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-(2-(2-methoxyethoxy)ethoxy)carbonylpropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

To a stirred solution of Reference Example 11 (0.329 g, 0.79 mmol), the acid Reference Example 26 (0.225 g, 0.95 mmol), triethylamine (0.079 g, 0.110 ml, 0.79 mmol) and HOBT (0.129 g, 0.95 mmol) in dichloromethane (10 ml) was added EDC (0.183 g, 0.95 mmol). The mixture was stirred for 48h and then the solution was dried and evaporated. The residue was purified by MPLC [5% MeOH/CH_2Cl_2 as eluant] to give a white solid (0.283 g, 62%).
^{1}H-NMR (300MHz, DMSO-d6): δ = 2.52 (d, 2H), 2.60 (dd, 1H), 2.85 (dd, 1H), 3.31 (s, 3H), 3.50 (m, 2H), 3.60 (m, 2H), 3.68 (m, 2H), 3.80 (m, 2H), 4.00 (dd, 1H), 4.10-4.40 (m, 5H), 4.54 (m, 2H), 4.76 (m, 1H), 5.15 (m, 1H), 5.64 (m, 1H), 6.09 (s, 1H), 6.43 (d, 1H), 7.43 (m, 2H), 7.58 (d, 1H) and 8.75 (d, 1H). MS: ESP$^+$ (M+H)$^+$ = 578.

Example 39: 5(R)-Isoxazol-3-yloxymethyl-3-(4-morpholino-3-fluoro-phenyl)oxazolidin-2-one

Prepared by the general method of Example 1 using as starting material 5(R)-hydroxymethyl-3-(4-morpholino-3-fluoro-phenyl)oxazolidin-2-one (WO95/07271; 300mg, 1.01mmol), 3-hydroxyisoxazole (95mg, 1.12mmol), diisopropylazodicarboxylate (225mg, 1.11mmol) and triphenylphosphine (305mg, 1.16mmol) in THF (5ml). Purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (7/3)) to give the title compound (254mg, 69%) as a colourless solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.05 (m, 4H), 3.88 (m, 4H), 3.94 (dd, 1H), 4.14 (t, 1H), 4.47-4.62 (m, 2H), 5.01 (m, 1H), 6.00 (d, 1H), 6.94 (t, 1H), 7.15 (dd, 1H), 7.46 (d, 1H), 8.15 (d, 1H). MS: ESP$^+$ (M+H)$^+$= 364.

Reference Example 27: 5(R)-Hydroxymethyl-3-(4-iodophenyl)oxazolidin-2-one

3-Phenyl-oxazolidin-2-one (U.S.Patent 4705799; 3.0g, 15.5mmol), silver trifluoroacetate (4.5g, 20.4mmol) and iodine (4.7g, 18.5mmol) in a mixture of acetonitrile (30ml) and chloroform (30ml) were stirred at room temperature for 72 hr then a further 1g silver trifluoroacetate and 1g iodine added and stirring continued for 18hr. The mixture was then filtered and the filtrate evaporated to give an orange oil which was purified by flash chromatography (Merck 9385 silica, 5% MeOH / dichloromethane) followed by recrystallisation from EtOAc / isohexane to give the title compound (1.85g, 38%) as a colourless solid. MS: ESP$^+$ (M+H)$^+$= 320.

^{1}H-NMR (300MHz, DMSO-d6): δ = 3.53 (m, 1H), 3.47 (m, 1H), 3.78 (dd, 1H), 4.05 (t, 1H), 4.69 (m, 1H), 5.18 (t, 1H), 7.38 (d, 2H), 7.69 (d, 2H).

Reference Example 28: 5(R)-Isoxazol-3-yloxymethyl-3-(4-iodophenyl)oxazolidin-2-one

Prepared by the general method of Example 1 using (1.85g, 5.80mmol), 3-hydroxyisoxazole (0.55g, 6.47mmol), diisopropylazodicarboxylate (1.29g, 6.39mmol) and triphenylphosphine (1.75g, 6.68mmol) in THF (30ml). Purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (1/1)) to give the title compound (1.45g, 64%) as a colourless solid. MS: ESP$^+$ (M+H)$^+$= 387.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.94 (dd, 1H), 4.13 (t, 1H), 4.46-4.61 (m, 2H), 5.03 (m, 1H), 6.00 (d, 1H), 7.34 (d, 2H), 7.69 (d, 2H), 8.15 (d, 1H).

Reference Example 29: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-tert-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)phenyl)oxazolidin-2-one

Lithium chloride (1.0g, 23.6mmol), triphenylarsine (0.95g, 3.10mmol) and tris(dibenzylideneacetone) dipalladium(0) (0.7g, 0.76mmol) were added at room temperature, under an atmosphere of nitrogen, to a stirred solution of Reference Example 28 (3.0g, 7.77mmol) in DMF (50ml, degassed). The resulting mixture was stirred for 15min then N-tert-butoxycarbonyl-4-trimethylstannyl-1,2,5,6-tetrahydropyridine (3.0g, 8.67mmol; prepared from N-tert-butoxycarbonyl-4-triflate-1,2,5,6-tetrahydropyridine (WO97/30995) reacted with hexamethyltin using a Pd(0) catalyst) in DMF (10ml) added in one go. The reaction was stirred and heated at 50°-55°C for 3hr, cooled to room temperature then treated with a 2N aqueous solution of potassium fluoride (8ml). After stirring for 30min the solvent was evaporated (50°, high vac.) then the residue partitioned between dichloromethane and water, filtered and the dichloromethane layer separated. Washed with water (2X) and sat. brine, dried over magnesium sulfate and evaporated to an orange viscous oil. Purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (3/2)) to give the title compound as a pale yellow solid. MS: ESP$^+$ $(M+H)^+$= 442.

Reference Example 30: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-phenyl)oxazolidin-2-one

Reference Example 29 (2.1g, 4.76mmol) in MeOH (30ml) (partial solution) was treated at room temperature with an approx. 4M solution of HCl in ethanol and the resulting mixture stirred 4hr then left to stand 16hr. Diethyl ether (50ml) was then added and the resulting pale yellow solid filtered, washed with ether and dried: 1.71g (95% yield) - title compound as the hydrochloride salt.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.66 (m, 2H), 3.30 (m, partially obscured by DMSO, 2H), 3.73 (m, 2H), 3.92 (dd, 1H), 4.20 (t, 1H), 4.41-4.53 (m, 2H), 5.08 (m, 1H), 6.16 (m, 1H), 6.35 (d, 1H), 7.49 (d, 2H), 7.57 (d, 2H), 8.68 (d, 1H), 9.30 (s(br), 2H). MS: ESP$^+$ $(M+H)^+$= 342. Free base isolated by treating with aqueous sodium hydroxide solution and extraction with dichloromethane to give title compound as a yellow solid.

Reference Example 31: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(R)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)phenyl)oxazolidin-2-one

1,3 Dicyclohexylcarbodiimide (298mg, 1.45mmol) was added in one go at room temperature to a stirred soltion of (R)-2,3-O-isopropylideneglyceric acid (235mg, 1.40mmol 87% purity) and 1-hydroxybenzotriazole (218mg, 1.42mmol) in dichloromethane (15ml). The resulting suspension was stirred 1hr then a further 5ml dichloromethane was added followed by Reference Example 30 (500mg, 1.47mmol), stirred 16hr, filtered and the filtrate washed with water and sat. brine. Purified by flash chromatography (Merck 9385 silica, 2.5% MeOH / dichloromethane) to give the title compound (395mg, 57%) as a colourless solid. MS: ESP$^+$ $(M+H)^+$= 470.

Reference Example 32: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)phenyl)oxazolidin-2-one

Prepared by the general method of Reference Example 31, using Reference Example 30 (500mg, 1.47mmol), 1,3 dicyclohexylcarbodiimide (298mg, 1.45mmol), (S)-2,3-O-isopropylideneglyceric acid (235mg, 1.40mmol 87% purity) and 1-hydroxybenzotriazole (218mg, 1.42mmol) in dichloromethane (15ml).Purified by flash chromatography (Merck 9385 silica, 2.5% MeOH / dichloromethane) to give the title compound (408mg, 59%) as a colourless solid. MS: ESP$^+$ $(M+H)^+$= 470.

Example 40: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)phenyl)oxazolidin-2-one

Prepared by the general method of Example 4 using Reference Example 31(395mg, 0.84mmol) in 1N hydrochloric acid (3ml) and THF (9ml). Purified by flash chromatography (Merck 9385 silica, 8% MeOH / dichloromethane) to give the title compound (203mg, 56%) as a colourlrss solid, mp=138°-144°C.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.40-2.56 (m, partially obscured by DMSO, 2H), 3.40-3.63 and 3.63-3.88 (m, 4H), 3.92 (dd, 1H), 4.11 (m, 2H), 4.20 (t, 1H), 4.30-4.54 (m, 3H), 4.68 (m, 1H). 4.92 (m, 1H), 5.07 (m, 1H), 6.15 (m, 1H), 6.37 (d, 1H), 7.46 (d, 2H), 7.53 (d, 2H), 8.68 (d, 1H). MS: ESP$^+$ $(M+H)^+$= 430.

Example 41: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)phenyl)oxazolidin-2-one

Prepared by the general method of Example 4 using Reference Example 32 (408mg, 0.87mmol) in 1N hydrochloric acid (3ml) and THF (9ml). Purified by flash chromatography (Merck 9385 silica, 8% MeOH / dichloromethane) to give the title compound (124mg, 33%) as a colourless solid, mp=200°-202°C(dec).

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.38-2.56 (2H), 3.20-3.40 (m, partially obscured by DMSO, 2H), 3.54 (m, 1H), 3.64-3.85 (m, 1H), 3.92 (dd, 1H), 4.12 (m, 2H), 4.20 (t, 1H), 4.30-4.55 (m, 3H), 5.07 (m, 1H), 6.15 (m, 1H), 6.37 (d, 1H), 7.46 (d, 2H), 7.53 (d, 2H), 8.66 (d,1H). MS: ESP$^+$ (M+H)$^+$= 430.

Example 42: 5(R)-Isoxazol-3-yloxymethyl-3-(4-methylthiophenyl)oxazolidin-2-one

Prepared by the general method of Example 1 using 5(R)-hydroxymethyl-3-(4-methylthiophenyl)oxazolidin-2-one (650mg, 2.72mmol; prepared from the reaction of 4-methylthioaniline and (R)-glycidyl butyrate), 3-hydroxyisoxazole (243mg, 2.86mmol), diisopropylazodicarboxylate (577mg, 2.86mmol) and triphenylphosphine (770mg, 2.94mmol) in THF (10ml).Purified by flash chromatography (Merck 9385 silica, EtOAc / isohexane (1/1)) to give the title compound 507mg, 61%) as a colourless solid. MS: ESP$^+$ (M+H)$^+$= 307.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.47 (s, 3H), 3.97 (dd, 1H), 4.15 (t, 1H), 4.47-4.62 (m, 2H), 5.02 (m, 1H), 6.00 (d, 1H), 7.30 (d, 2H), 7.49 (d, 2H), 8.14 (d, 1H).

Example 43: 5(R)-Isoxazol-3-yloxymethyl-3-(4-methylsulfinylphenyl)oxazolidin-2-one and Example 44: 5(R)-Isoxazol-3-yloxymethyl-3-(4-methylsulfonylphenyl)oxazolidin-2-one

3-Chloroperoxybenzoic acid (282mg,70% strength, 1.14mmol) was added to a solution of Example 42 (340mg, 1.11mmol) in dichloromethane (10ml) at -40°C. The reaction was stirred at -30° to -40°C for 3hr then diluted with more dichloromethane (10ml), washed with aq. sodium bisulfite solution, sat. aq. sodium bicarbomate solution and water, dried over magnesium sulfate and evaporated to a colourless oil. Purified by flash chromatography (Merck 9385 silica, 5% MeOH / dichloromethane) to give Example 43 (275mg, 77%) and Example 44 (31mg), both as colourless solids.

Example 43: MS: ESP$^+$ (M+H)$^+$= 323.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.73 (s, 3H), 4.06 (dd, 1H), 4.22 (t, 1H), 4.50-4.65 (m, 2H), 5.08 (m, 1H), 6.00 (d, 1H), 7.69 (d, 2H), 7.77 (d, 2H), 8.15 (d, 1H).

Example 44: MS: ESP$^+$ $(M+H)^+$= 339.

^{1}H-NMR (300MHz, DMSO-d6): δ = 3.14 (s, 3H), 3.98 (dd, 1H), 4.26 (t, 1H), 4.43-4.54 (m, 2H), 5.10 (m, 1H), 6.34 (d, 1H), 7.80 (d, 2H), 7.92 (d, 2H), 8.66 (d, 1H).

Example 45: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-(1-imidazoyl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)-oxazolidin-2-one

Reference Example 19 (200mg, 0.45mmol) and 1H-imidazole (34mg, 0.50mmol) in 2-propanol (2ml)were refluxed for 8hr then the resulting solution cooled to room temperature and purified by flash chromatography (Merck 9385 silica, 10% MeOH / dichloromethane) to give the title compound (83mg, 36%) as a colourless solid.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.25-2.50 (m, 2H), 3.55-3.83 (m, 2H), 3.95 (dd, 1H), 4.00-4.40 (m, 5H), 4.44-4.56 (m, 2H), 4.56-4.68 (m, 1H), 5.11 (m, 1H), 5.65 (d) and 5.75 (d) (1H), 5.87 (m, 1H), 6.37 (d, 1H), 6.85 (m, 1H), 7.15 (m, 1H), 7.36 (d, 2H), 7.58 (m, 1H), 8.68 (d,1H). MS: ESP$^+$ $(M+H)^+$= 516.

Example 46: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(R,S)-hydroxy-3-(1,2,4-triazol-1-yl)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)-oxazolidin-2-one

Prepared by the general method of Example 45 using Reference Example 19 (200mg, 0.45mmol) and 1H-1,2,4-Triazole (35mg, 0.50mmol) in 2-propanol (2ml). Purified by flash chromatography (Merck 9385 silica, 10% MeOH / dichloromethane) to give the title compound (84mg, 36%) as a colourless solid. MS: ESP$^+$ $(M+H)^+$= 517.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.25-2.50 (m, 2H), 3.55-3.85 (m, 2H), 3.95 (dd, 1H), 4.00-4.40 (m, 5H), 4.40-4.55 (m, 2H), 4.68-4.82 (m, 1H), 5.12 (m, 1H), 5.77 (d) and 5.81 (d) (1H), 5.90 (m, 1H), 6.77 (d, 1H), 7.35 (d, 2H), 7.95 (s, 1H), 8.44 (s, 1H), 8.68 (d, 1H).

Example 47: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-acetoxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

(S)-2-Acetoxypropionyl chloride (126mg, 0.84mmol) was added dropwise at room temperature to a stirred suspension of Reference Example 11 (300mg, 0.76mmol) and N,N

diisopropyl ethylamine (210mg, 1.63mmol) in dichloromethane (10ml). The reaction was stirred at room temperature for 2hr then purified by flash chromatography (Merck 9385 silica, 2.5% MeOH / dichloromethane) to give the title compound (322mg, 90%) as a colourless solid. MS: ESP$^+$ (M+H)$^+$= 474.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.48 (s) and 1.51 (s) (3H), 2.14 (s, 3H), 2.50-2.74 (m, 2H), 3.68 (m) and 3.96 (m) (3H), 4.05-4.36 (m, 3H), 4.47-4.62 (m, 2H), 5.04 (m, 1H), 5.35-5.55 (m, 1H), 5.97 (m, 1H), 6.00 (d, 1H), 7.20-7.30 (m, 2H), 7.45 (d, 1H), 8.15 (d, 1H).

Example 48: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Example 47 (200mg, 0.42mmol) in 10ml of a saturated solution of ammonia in MeOH was stirred at room temperature for 18hr then cooled in ice-water before filtering the resulting colourless solid. Washed with ice-cold MeOH and diethyl ether then dried to give the title compound (156mg, 86%). MS: ESP$^+$ (M+H)$^+$= 432.

^{1}H-NMR (300MHz, DMSO-d6): δ = 1.23 (s) and 1.25 (s) (3H), 2.33-2.50 (m, 2H), 3.52-3.85 (m, 2H), 3.93 (dd, 1H), 4.02-4.38 (m, 3H), 4.40-4.60 (m, 2H), 4.85-5.00 (m, 1H), 5.11 (m, 1H), 6.03 (m, 1H), 6.38 (d, 1H), 7.33 (dd, 1H), 7.41 (t, 1H), 7.52 (dd, 1H), 8.68 (d, 1H).

Example 49: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-acetoxyacetyl-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 6 using Reference Example 11 (300mg, 0.76mmol), acetoxyacetyl chloride (114mg, 0.83mmol), triethylamine (88mg, 0.87mmol) and 4-(dimethylamino) pyridine (25mg) in dichloromethane 10ml). Purified by chromatography (bond elut (silica, 10g), 1-2% MeOH / dichloromethane) to give the title compound (230mg, 66%) as a colourless solid. MS: ESP$^+$ (M+H)$^+$= 460.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.50-2.66 (m, 2H), 3.60 (t) and 3.83 (t) (2H), 3.96 (dd, 1H), 4.10 (m) and 4.24 (m) (2H), 4.15 (t, 1H), 4.50-4.64 (m, 2H), 4.77 (s) and 4.81 (s) (2H), 5.04 (m, 1H), 5.90-6.00 (m, 1H), 6.00 (d, 1H), 7.21-7.30 (m, 2H), 7.45 (d, 1H), 8.15 (d, 1H).

Example 50: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-hydroxyacetyl-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 48 using Example 49 (170mg, 0.37mmol) in 10ml of a saturated solution of ammonia in MeOH to give the title compound (121mg, 79%) as a colourless solid. MS: ESP$^+$ $(M+H)^+$= 418.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.52-2.62 (m, 2H), 3.48 (t) and 3.65 (t) (2H), 3.87 (t) and 3.95 (m) (3H), 4.16 (t, 1H), 4.22 (dd, 1H), 4.30 (m, 1H), 4.48-4.62 (m, 2H), 5.04 (m, 1H), 5.92 (m) and 6.00 (m) (1H), 6.00 (d, 1H), 7.20-7.30 (m, 2H), 7.43 (d, 1H), 8.15 (d, 1H).

Example 51: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(3-pyridin-1-iummethyl-benzoyloxy)-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one chloride

Example 12 (0.40g, 0.89mmol) was suspended in dichloromethane (20ml), and pyridine (0.07g, 0.89mmol), 4-dimethylaminopyridine (0.2g) was added. 3-chloromethylbenzoyl chloride was added dropwise and the reaction mixture was stirred at room temperature for 2hr. The resulting solution was washed with water, dried ($MgSO_4$) and purified by chromatography (Merck 9385 silica, 5-10% MeOH in CH_2Cl_2) to give the title compound as a pale yellow solid (0.30g, 42%) after trituration with diethyl ether.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.43 (partially obscured by DMSO, 2H), 3.64- 4.52 (m, 10H), 4.74 (m, 1H), 5.08 (m, 1H), 5.98 (m,3H), 6.37 (m, 1H), 7.35 (m, 2H), 7.46- 7.63 (m, 2H), 7.81 (m, 1H), 8.00 (m, 1H), 8.16 (m, 2H), 8.54- 8.65 (m ,2H), 8.68 (m,1H), 9.26 (M, 2H). MS: ESP$^+$ $(M)^+$ = 643

Example 52: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(3-chloromethyl-benzoyloxy)-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Example 12 (0.50g, 1.12M) was suspended in dichloromethane (20ml), and triethylamine (0.11g, 0.16mmol) was added. 3-chloromethylbenzoyl chloride was added dropwise and the reaction mixture was stirred at room temperature for 2hr. The resulting solution was washed with water, dried ($MgSO_4$) and purified by chromatography (Merck 9385 silica, 4-5% MeOH in CH_2Cl_2) to give the title compound as a yellow solid (0.46g, 69%) after trituration with diethyl ether and isohexane, also containing some di- substituted derivative.

¹H-NMR (300MHz, DMSO-d6): δ = 2.45 (partially obscured by DMSO, 2H), 3.65- 3.98 (m, 3H), 3.98- 4.25 (m, 2H), 4.31- 4.55 (m, 4H), 4.70- 4.87 (m, 4H), 5.07 (m, 1H), 5.71 (m, 1H), 6.04 (m, 1H), 6.41 (m, 1H), 7.28- 7.46 (m, 2H), 7.46- 7.59 (m, 2H), 7.71 (m, 1H), 7.87- 8.12 (m, 2H), 8.72 (m, 1H). MS: ESP^+ $(M+H)^+$ = 600.

Example 53: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(3-morpholinomethyl-benzoyloxy)-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Example 52 (0.10g, 0.17mmol), was stirred in DMF (3ml), sodium iodide (ca. 10mg) and morpholine (0.07g, 0.67mmol) was added and the reaction mixture was heated at 50°C for 5hr. The DMF was removed by evaporation and the residue was taken up in dichloromethane, washed with water, dried ($MgSO_4$) and purified by chromatography (Merck 9385 silica, 5-10% MeOH in CH_2Cl_2) to give the title compound as an off white solid (65mg, 60%), after trituration with isohexane and diethyl ether.

¹H-NMR (300MHz, DMSO-d6): δ = 2.27 (m, 4H), 2.41 (partially obscured by DMSO, 2H), 3.40- 3.59 (m, 6H), 3.63- 3.98 (m, 3H), 3.98- 4.57 (m, 7H), 4.74 (m, 1H), 5.08 (m, 1H), 5.67 (m, 1H), 6.04 (m, 1H), 6.39 (m, 1H), 7.28- 7.64 (m, 5H), 7.88 (m, 2H), 8.72 (m, 1H). MS: ESP^+ $(M+H)^+$ = 651.

Example 54: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(3-(4-methylpiperazinomethyl)benzoyloxy)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 53, using Example 52 (0.10g, 0.17mmol), sodium iodide (ca. 10mg) and N-methylpiperazine (0.07g, 0.67mmol). Purified by chromatography (Merck 9385 silica, 5-10% MeOH in CH_2Cl_2- 10% MeOH + 1% ammonia in CH_2Cl_2), to give the title compound as white solid (55mg, 50%) after trituration with isohexane.

¹H-NMR (300MHz, DMSO-d6): δ = 2.44 (partially obscured by DMSO, 5H), 2.62 (m, 4H), 3.21- 3.35 (partially obscured by water, 4H), 3.55 (m, 2H), 3.65- 3.84 (m, 2H), 3.92 (dd, 1H), 4.08- 4.25 (m, 2H), 4.34 (m, 1H), 4.45 (m, 4H), 4.75 (m, 1H), 5.08 (m, 1H), 5.62 (m, 1H), 6.02 (broad s, 1H), 6.36 (m, 1H), 7.28- 7.60 (m, 5H), 7.88 (m, 2H), 8.68 (m, 1H). MS: ESP^+ $(M+H)^+$ = 664.

Example 55: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-(3-di-n-butylaminomethylbenzoyloxy)propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Prepared by the general method of Example 53, using Example 52 (0.10g, 0.17mmol), sodium iodide (ca. 10mg) and di-N-butylamine (0.07g, 0.67mmol). Purified by chromatography (Merck 9385 silica, 5-10% MeOH in CH_2Cl_2- 10% MeOH + 1% ammonia in CH_2Cl_2), to give the title compound as white solid (54mg, 47%) after trituration with isohexane.

^{1}H-NMR (300MHz, DMSO-d6): δ = 0.71-0.89 (m, 6H), 1.13-1.43 (m, 8H), 2.31 (partially obscured by DMSO, 6H), 3.33 (partially obscured by water, 2H), 3.42- 3.59 (m, 2H), 3.67-3.97 (m, 3H), 3.97- 4.56 (m, 5H), 4.74 (m, 1H), 5.08 (m, 1H), 5.67 (m, 1H), 6.03 (broad s, 1H), 6.38 (m, 1H), 7.28- 7.63 (m, 5H), 7.87 (m, 2H), 8.69 (m, 1H). MS: ESP$^+$ $(M+H)^+$ = 693.

Example 56: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-n-propyl-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

Reference Example 11 (500mg, 1.26mmol) was stirred in MeOH (10ml) and glacial acetic acid (~0.5ml) was added to pH4. Propanal (80.7mg, 1.39mmol) was added dropwise, and the reaction was stirred for 40 minutes. To the stirred solution, sodium cyanoborohydride was added (83.4mg, 1.33mmol) portionwise. The reaction was stirred for a further 30 minutes at room temperature. The reaction was quenched with 10% NaOAc and extracted with dichloromethane and the combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting brown oil was triturated with ether to yield the title compound as an orange solid (300.6mg, 59%). MS: ESP+ $(M+H)^+$ = 402.

^{1}H-NMR (300MHz, DMSO-d6): δ = 0.85 (t, 3H), 1.46 (m, 2H), 2.32 (t, 2H), 2.40 (broad s, 2H), 2.57 (t, 2H), 3.04 (d, 2H), 3.93 (dd, 1H), 4.19 (t, 1H), 4.48 (m, 2H), 5.08 (m, 1H), 5.97 (broad s, 1H), 6.37 (d, 1H), 7.29-7.40 (m, 2H), 7.49 (dd, 1H), 8.70 (d, 1H).

Example 57: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2-hydroxyethyl)-1,2,5,6-tetrahydropyrid-4-yl)-3-fluorophenyl)oxazolidin-2-one

To a stirred partial solution of Reference Example 11 (318mg, 0.80mmol) and $NaHCO_3$ (169mg, 2.01mmol) in ethanol (5ml) under an atmosphere of nitrogen, 2-bromoethanol (151mg, 1.21mmol) was added dropwise. The reaction was then refluxed for 20 hours. Water